THE

AMERICAN JOURNAL

OF THE

MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.
EDITOR

RICHARD A. KERN, M.D.
ASSISTANT EDITOR

NEW SERIES

VOL. 195

LEA & FEBIGER
PHILADELPHIA
1938

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1938

PRINTED IN U. S. A.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
JANUARY, 1938

ORIGINAL ARTICLES.

THE PLACENTA AS A MODIFIED ARTERIOVENOUS FISTULA, CONSIDERED IN RELATION TO THE CIRCULATORY ADJUSTMENTS TO PREGNANCY.*

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During pregnancy changes take place in the maternal circulation. In this paper, it is proposed to present certain data concerning the circulatory adjustments to pregnancy and to consider certain mechanisms by which these changes may be brought about.

In recent years, studies of the circulation during pregnancy have been made by various workers. With certain important exceptions, which will be noted, the observations presented here were made by my colleagues and myself in a study of pregnant women during the past 5 years and many of these data are derived from the study of 4 young women during the last 6 months of pregnancy and varying periods of the puerperium.[5] The circulatory adjustment to pregnancy has been found to include the following:

1. The heart rate is elevated (Fig. 1, *A*). There is an increase in the basal heart rate of 12 to 20 beats per minute. This amounts to some 20,000 extra beats per day and to a total of over 4,000,000 during the last 200 days of the gravid period.

2. The arterial blood pressure, on the average, is decreased, but the change is not great (Fig. 1, *B*). The decrease in diastolic pressure is slightly more than the decrease in systolic pressure, so that the pulse pressure rises. Our own observations on this point have

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* Read before the section on Pathology and Physiology at the eighty-eighth annual session of the American Medical Association meeting, Atlantic City, N. J., June 10, 1937.

recently been supported by the more extensive ones of Landt and Benjamin.[10]

3. The total oxygen absorbed by the mother's lungs, and transported to her own body and that of the fetus, is increased. This increase is gradual and reaches a point 15 to 20% above the non-pregnant level (Fig. 1, *C*).

4. The cardiac output per minute is increased. In Fig. 1, *D*, the cardiac output per minute (in a representative case) is charted against the oxygen consumption. It is seen: *a*, That the cardiac output per minute exceeds the non-pregnant level by about the fourth month; *b*, that the increase in output is greater than the rise in oxygen consumption (this disproportion implies a fall in the arteriovenous oxygen difference); *c*, that in the last weeks of pregnancy the cardiac output per minute changes toward the normal, *i. e.*, it falls. This takes place at a time when the fetus is increasing in size and when the total absorption of oxygen is not reduced.

5. The venous blood pressure of pregnant women is elevated in a particular area of the body, the pelvis and legs (Fig. 1, *E*. In pregnant women the venous pressure in the femoral vein is usually 100 to 200 mm. of water higher than in the arm, *i. e.*, from 2 to 3 times normal. In normal individuals, arm and leg pressures are approximately identical. We were led to make this observation by a visible network of veins which appeared over the abdomen and was sufficiently impressive to suggest a collateral circulation. Observations on pregnant bitches indicated that these changes in venous pressure are not due to an increase in general intraäbdominal pressure, and that they are only partly explained by the local pressure of the gravid uterus on the veins. Moreover, in these animals the venous pressure was higher as the point of measurement approached the placentæ.

6. Blood was drawn from the uterine veins of pregnant bitches and the oxygen saturation determined. Some variation was found, but in general (5 out of 6 times) the blood leaving the gravid uterus contained more oxygen than blood from the right ventricle. This is to say that in pregnancy the blood irrigating the placental and uterine structures exhibits a low arteriovenous difference. Barcroft[1] has made similar comparisons in rabbits and finds a similar situation in early pregnancy. As the time of delivery approached, the oxygen saturation of this blood diminished and at term was quite low. Barcroft points out that in many animals the saturation of the blood going to the fetus is higher than that of normal venous blood.

7. The total blood volume, according to the recent studies by Thomson, Hirsheimer, Gibson and Evans[17] is increased (Fig. 1, *F*). This increase in their patients amounted to some 42%. Like the cardiac output, the total blood volume diminished in the last weeks of pregnancy. Probably this fall in blood volume is concerned in

the changes in heart rate, blood pressure and cardiac output which occur in the last month of pregnancy.

8. Over the placenta is heard a loud murmur. When well heard this is a continuous bruit with a systolic accentuation.

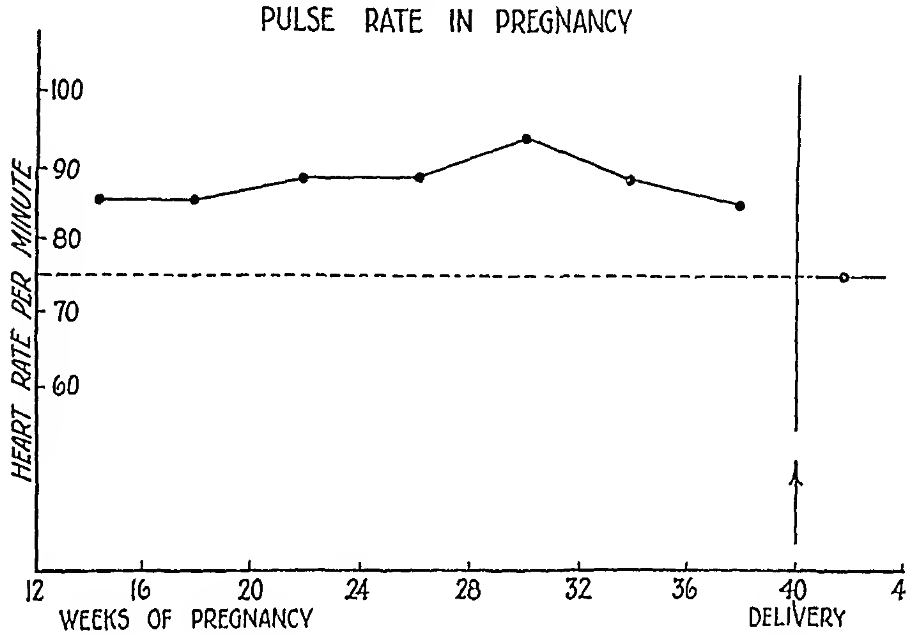

Fig. 1 *A*

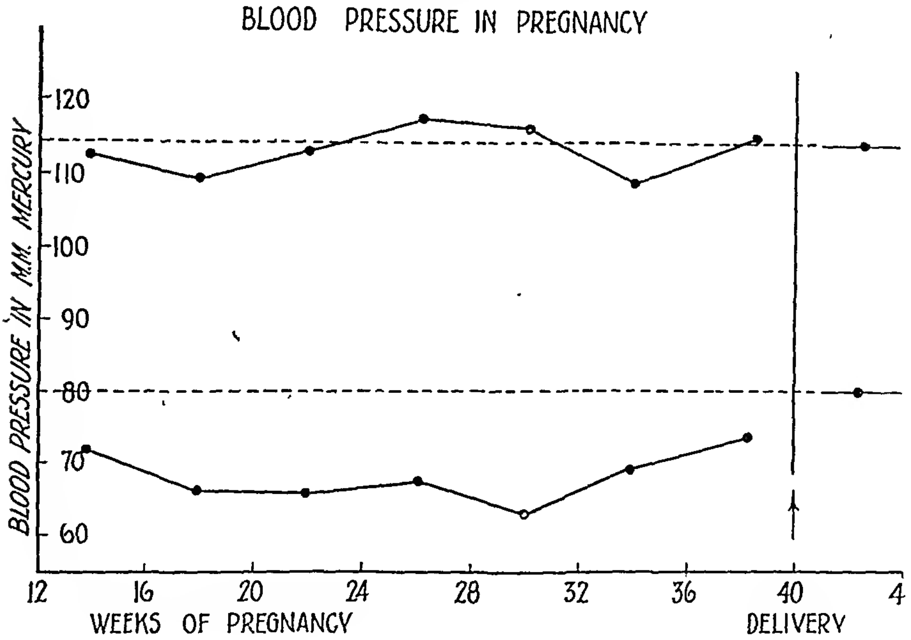

Fig. 1 *B*

The major alterations in the circulation of pregnant women thus include: 1, An increase in heart rate; 2, a fall in the diastolic blood pressure; 3, an increase in the cardiac output out of proportion to the increase in oxygen consumption; 4, an elevated venous pressure in pelvis and legs; 5, a relatively high oxygen content in the blood leaving the uterus; 6, an increase in total blood volume; 7, a loud bruit over the placenta.

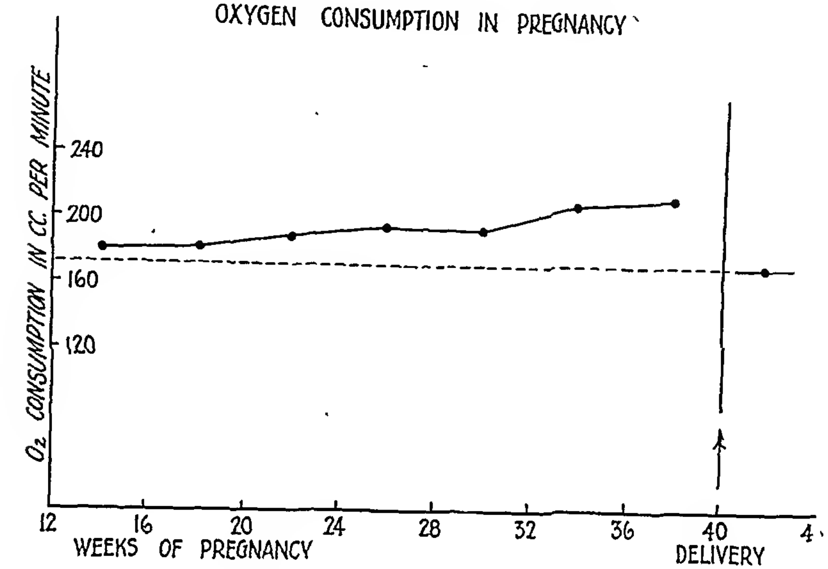

FIG. 1 *C*

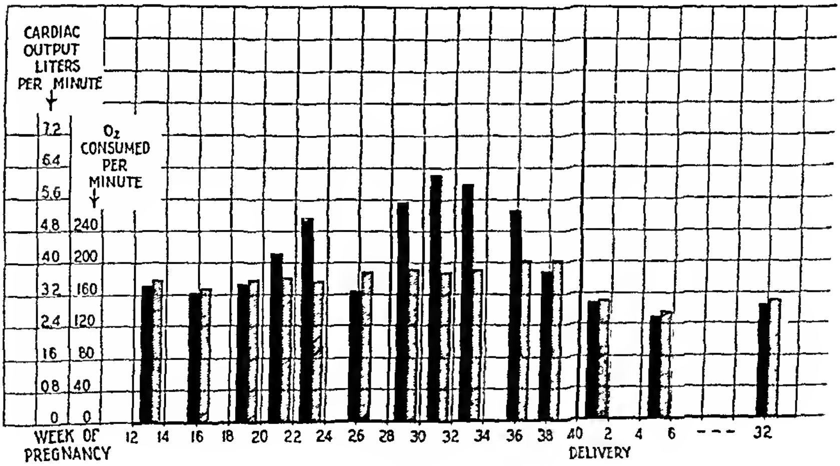

FIG. 1 *D*

In such an intricate series of events as the pregnant state there must be many factors which may influence the circulation. On the basis of the observations here reported, two such factors suggest themselves as of particular importance. One of these is the obstruction offered by the enlarging uterus to the return of blood from the legs. This is demonstrable and many of its effects are known. The other factor to be discussed is concerned with the large blood supply to the placenta. One is struck by the similarity of the changes observed in pregnant women to those known to occur in patients with a large arteriovenous connection or fistula. The circulation in patients

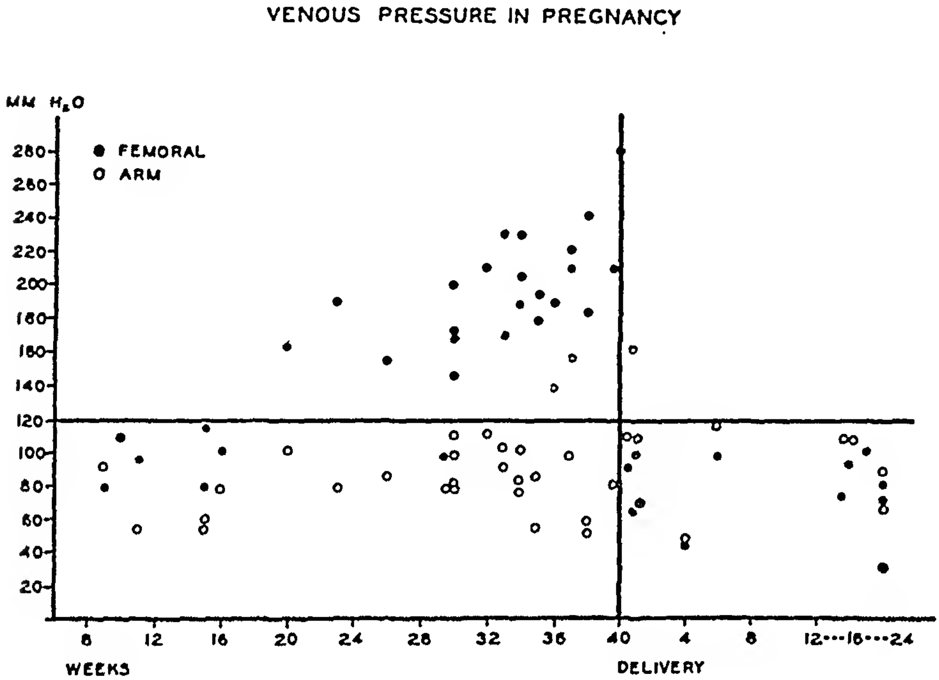

FIG. 1 *E*

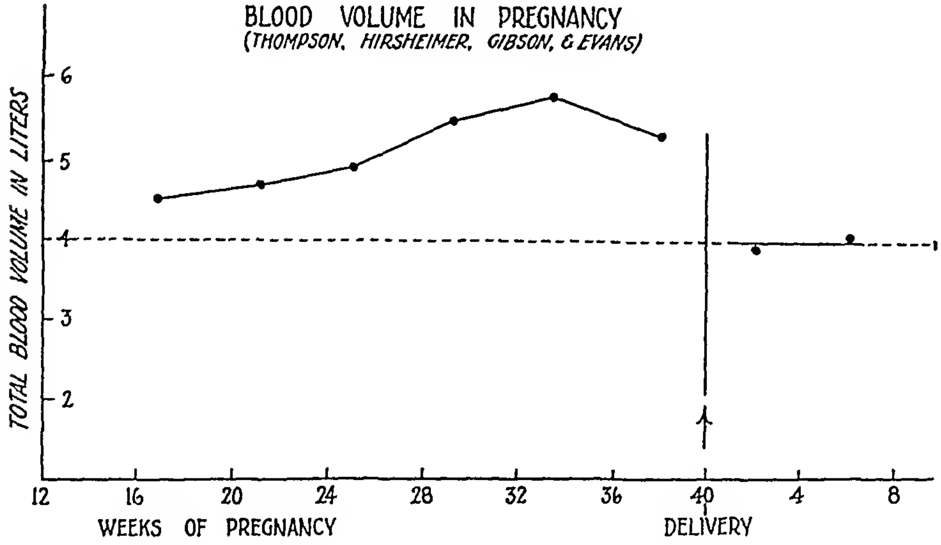

FIG. 1 *F*

FIG. 1.—*A*, Pulse rate in pregnancy; *B*, blood pressure in pregnancy; *C*, oxygen consumption in pregnancy; *D*, the cardiac output and total oxygen consumption during pregnancy and the puerperium (the solid columns represent the cardiac output; the barred columns, the oxygen consumption); *E*, venous pressure in pregnancy (solid circles, femoral vein; hollow circles, arm vein); *F*, blood volume in pregnancy.

with arteriovenous fistula has been studied by Halsted,[7] Reid,[14] Lewis and Drury,[12] Harrison, Dock and Holman,[8] Holman,[9] Matas,[13] Brown,[3] Ellis and Weiss,[6] Smith,[15] Blumgart and Ernstene,[2] Laplace,[11] Burwell and Kennedy,[4] and others. Such patients or animals may exhibit the following: 1, tachycardia, 2, increased pulse pressure (which may be associated with peripheral signs comparable to those in patients with aortic regurgitation), 3, an increase in the cardiac output per minute, 4, a decrease in the arteriovenous oxygen difference, 5, an elevated pressure in the veins adjacent to the fistula, 6, a higher oxygen saturation of the blood in these veins than in the mixed venous blood, 7, an increase of the total blood volume, 8, a continuous bruit with systolic accentuation, heard in the region near the fistula, 9, dilatation of the artery leading to the fistula, proximal to the point of leakage.

These phenomena, excepting the last, have been shown to be present in pregnant women, although not always in as striking a degree as they may exhibit when they occur in association with arteriovenous fistula.

During recent months Dr. Kennedy and I have studied a young man with several arteriovenous fistulas in his left arm. Table 1 offers a comparison of certain aspects of his circulation with the findings in normals and in pregnant women. The similarities between the phenomena manifested in this boy (most of which could be abolished by compressing the fistula) and those in pregnant women speak for themselves.

TABLE 1.—COMPARISON OF THE CHANGES IN THE CIRCULATION IN PREGNANCY AND IN ARTERIOVENOUS FISTULA.

	Normal.	Arteriovenous fistula.	Pregnancy.
Continuous bruit . .	Absent	Present	Present
Average basal heart rate .	66 to 70 per minute	82 per minute	90 per minute
Arteriovenous oxygen difference	55 to 70 cc. per liter	38 to 46 cc. per liter	40.5 cc. per liter
Cardiac output per square meter per minute . .	2 to 2.4 liters	3.2 liters	2.9 liters
Oxygen content of venous blood near fistula . .	At level of venous blood	Near level of arterial blood	Between levels of arterial and venous blood
Pressure in veins near fistulous opening . . .	Normal	High	High
Total blood volume . .	Females, 4300 cc. Males, 5300 cc.	6900 cc.	5300 cc.
Arterial blood pressure (mm. Hg)	$\frac{110\text{–}120}{70\text{–}80}$	102/56	112/70
Dilatation of artery proximal to leak . . .	Absent	Present	Present

Among the other factors which may influence the circulation during pregnancy, the activity of the maternal thyroid is to be considered. The present evidence appears to indicate that thyrotoxicosis is at most only a minor factor in the circulatory changes in normal pregnancy.

It is now necessary to consider whether the structure of the placenta is compatible with the hypothesis that an arteriovenous shunt occurs within it. An instructive and recent description of the vascular systems of the placenta is that of Spanner.[16] This exhaustive treatise demonstrates that in the placenta arteries connect with veins by way of relatively large vascular spaces and without the interposition of either arterioles or capillaries. Several hundred arteries with a terminal diameter averaging 0.15 mm. empty directly (like the nozzle of a hose) into the intervillous space. In the light of Halsted's[7] work on arterial dilatation proximal to the arteriovenous leak it is of great interest that Spanner has showed that the arteries emptying into the intervillous space are dilated for a short distance proximal to the point of emptying.

Blood escapes from the intervillous space, according to Spanner, by flowing into the marginal sinus through relatively wide openings. The structure of the maternal vascular system in the placenta thus offers a connection between arteries and veins which has both similarities to and differences from a simple arteriovenous shunt. The similarities have been pointed out. The differences in the main are two: 1, Between artery and vein there are interposed the tortuous channels of the intervillous space. 2, The venous blood flowing from the placenta enters a venous reservoir in which the pressure is already high because of the obstruction offered by the uterus to the venous return from legs and pelvic region. It is possible that these two factors may influence the manner and extent of the leakage of blood and pressure through the placenta, and therefore, the degree to which the circulation of the pregnant woman presents the changes characteristic of the presence of an arteriovenous fistula.

Conclusion. The demonstrated phenomena of the circulation in pregnant women plus the evidence offered by the structure of the placenta lead to the following conclusions:

The changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms:

1. Obstruction to venous return by the enlarged uterus.
2. An arteriovenous leak through the placenta.

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SERIAL BLOOD AND BONE MARROW FINDINGS OF AN EIGHT-MONTH PREMATURE AND ITS ROENTGEN RAY TREATED CHRONIC, MYELOID LEUKEMIC MOTHER.

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Leukemia complicated by pregnancy is a comparatively rare condition, as is indicated by the fact that only 30 cases have been reported in the literature.[1,3,4,13,16,18,20,25,27,28,32,37,38] In spite of its rarity, many interesting problems are encountered when a case of this sort presents itself. In this report we consider the various problems that arose in the care of a female patient suffering from chronic, myeloid leukemia, both before and after the induced delivery of an 8-month premature infant, also those arising from our opportunity to perform frequent blood and bone marrow examinations in both the mother and offspring.

Case History. B. L., aged 33, was first seen at the tumor clinic of the Jewish Hospital on September 15, 1935, complaining of weakness and loss of weight (from 205 to 165 lbs.) during the preceding 7 months. For about 5 months she had had a dragging pain in the left upper quadrant and had been conscious of a mass in the left hypochondrium. She bruised easily, and her menses, which were previously normal, had become rather painful and the flow quite abundant. Her appetite was good but she felt full after a few mouthfuls of food. Her past and family history were essentially negative. She had had 5 children during the past 12 years, all of whom are living and well.

Physical examination revealed a pale, well-developed female who lost considerable weight. The lymph nodes were not palpable. The spleen was enormous, occupying the entire left side of the abdomen and extending into the pelvis and across the midline. The liver was smooth and firm, its border extending 3 fingerbreadths below the costal margin. The urine was normal. Blood: the red blood cell count, 2,750,000; white blood cell count, 310,000, the white cells being predominantly myeloid (Table 1).

Roentgen Examination. The bones showed no abnormalities. A gastrointestinal series revealed the typical findings of enlarged spleen, *viz*, displacement of the stomach to the right and anteriorly, and downward displacement of the splenic flexure of the colon.[5]

Course. Roentgen treatment was instituted, September 20, 1935. The response to irradiation was quite satisfactory and prompt. A blood transfusion of 500 cc. was given on September 30, to hasten convalescence. The spleen gradually decreased in size until it could be barely felt under the costal margin. In January, 1936, because of the marked discomfort associated with the profuse menstrual periods, it was decided that sterilization should be performed. The patient was given a total dose of 560 r units (120 kv., 5 ma., 3 mm. Al) over the hypogastric region in a period of 2 weeks. Menstruation ceased and the Roentgen ray treatment was discontinued. Her course was uneventful until August, 1936, when a decided rise in the white cell count occurred. A small dose of irradiation was administered

(1800 r units) which tended to control the rise. Amenorrhea was constant and symptoms of pregnancy were not noted by the patient. In December, 1936, she returned with a rising white count, marked weakness, and feeling of pressure in the lower abdomen. Again Roentgen ray therapy (1800 r units) readily stopped the symptoms, but the diagnosis of a pregnancy was confirmed by a Roentgen ray examination which disclosed a 5½ to 6 months' fetus. Since the fetus had been exposed to the Roentgen ray, there was a possibility that some permanent damage had been incurred (Harris[12]), and it was felt that an abortion was indicated. Admission was unavoidably delayed until February 12, 1937; 6 weeks after confirmation of pregnancy. After medical induction failed, labor was induced surgically (rupture of the membranes, packing of cervix, etc.). Forty hours later, after an uneventful labor, the patient was delivered of a 5 lbs. 13 oz. premature (or immature if the criteria of Schultz[29] are used) male infant, living and well.

Complete blood counts of the mother's, infant's and cord blood were made immediately after delivery. Marrow punctures of the sternum and tibia of the infant were also performed at this time (Tables 1 to 5).

TABLE 1.—BLOOD CELL COUNTS OF THE MOTHER.

(Between September, 1935, and September, 1936, the patient received 5700 r units over the spleen and vertebral column, reducing the peripheral white blood count from 300,000 to 30,000 per c.mm.)

	10–29–36.	11–9.	2–10–37.	2–16.	2–23.	2–28.	3–21.	4–19.	5–28.	6–20.	6–29.	7–20.	7–21.*
Normoblasts . . .	..	2	..	1									
Myeloblasts . . .	..	..	..	3	1	..	..	7	4	4	2	65	
Myelocytes, neut. .	16	19	12	13	37	10	10	24	7	16	14	17	
Non-seg. neutrophils .	22	31	28	19	32	39	15	17	6	5	9	7	
Segmented neutrophils	50	30	46	50	15	38	45	22	70	61	55	7	
Metamyelocytes . .	..	..	..	..	..	..	..	10					
Myelocytes, eos. . .	..	..	..	..	1	..	..	1	2	.	1		
Eosinophils . . .	2	5	1	2	2	4	5	3	2	2	1	2	
Myelocytes, baso. .	..	..	..	2	..	3	..	2					
Basophils	..	15	9	6	7	4	14	8	9	3	8	1	
Lymphocytes . . .	10	..	3	5	2	2	6	4	..	7	9	1	
Monocytes . . .	..	..	1	..	2	..	5	2	..	2	1		
Endothelial cell . .	..	..	..	..	1								
Hemoglobin, % . .	..	..	80.0	81.0	76.0	62.0	72.0	77.0	70.0	68.0	66 0	65.0	
R.B.C. (in millions) .	..	..	4.1	4.2	3.7	3.6	4.0	4.2	4.4	3.5	3.4	3.2	
W.B.C. (in thousands)	44.0	67.0	34.4	62.8	94.5	50.2	22.3	48.0	33.4	9.9	6.1	48.2	54.4
Platelets (in thous.) .	..	..	920.0	700.0	420.0	670.0	410.0	910.0	460.0	580.0	640.0	70.0	

* Day of death.

Received 1800 r units of Roentgen ray between 12–10–36 and 12–31–36.

Received 2000 r units of Roentgen ray between 2–23–37 and 2–28–37.

Received 1200 r units of Roentgen ray between 5–16–37 and 6–20–37.

Received 2025 mg. hr. of radium over spleen 7–19–37.

The postpartum course of the mother was normal except for a slight increase in the activity of the leukemic process one week after delivery which was easily controlled by Roentgen treatments. Later Fowler's solution was administered and this readily controlled the patient's white blood cell count until 3 months after delivery.

Mother's Condition. At that time, the white cell count increased, the spleen began to enlarge, and the liver and peripheral lymph nodes began to enlarge for the first time. Roentgen ray therapy was again instituted (1200 r units over spleen and lumbar region during a 4-week interval) and a leukopenic phase developed. The white cell count dropped from 30 to 50,000 to 5 to 10,000. Transfusions were given twice a week for 5 weeks, and the leukocythemic stage returned (75,000 white blood cells). Radium over the spleen (2025 mg. hrs.) did not affect this appreciably.

The patient died 7 months after delivery with typical acute leukocythemic myeloblastic leukemia. The platelets were markedly reduced before death, and a bone marrow puncture, 20 hours before death, revealed no megakaryocytes. The postmortem revealed the typical picture of myeloblastic leukemia; a huge liver and spleen with enlargement of all lymph nodes and purpuric lesions throughout most of the body. The microscopic tissue sections revealed the usual leukemic infiltrative findings with a hyperplastic myeloblastic bone marrow.

TABLE 2.—CELL COUNTS OF MATERNAL BONE MARROW.

	2–10–37.	2–27.	7–21.
Megaloblast	0	0	0
Erythroblasts	4	1	0
Normoblasts	15	8	2
Myeloblasts	7	14	62
Myelocytes, neutrophils	50	38	14
Non-segmented neutrophils	11	6	11
Segmented neutrophils	11	6	9
Myelocytes, eosinophils	7	16	
Eosinophils	1	12	
Myelocytes, basophils	2	1	1
Basophils	2	1	
Lymphocytes	1	..	1
Monocytes	2	1	
Megakaryocytes	6	5	0
Total nucleated cells (in thous.) (per c.mm.)	176	450	341
Megakaryocytes (per c.mm.)	396	970	None found. Day of death.

Discussion. The first question that naturally arises in cases of leukemia complicated by pregnancy is the advisability of abortion. Many factors had to be considered, such as the leukemic process *per se* (whether chronic or acute, myeloid or lymphatic), the legal and extralegal implications. From the literature, it would appear that abortion is preferable, in the opinion of most, if the pregnancy is diagnosed early. If, however, it is well advanced, conflicting opinions occur. Some believe the pregnancy should be terminated because the treatment necessary to control the leukemia may injure the fetus; or that pressure and obstructive symptoms may develop in the mother from an enlarged liver, spleen and uterus. Others feel that pregnancy should go to term, since patients have been reported to have uneventful delivery and postpartum courses. It is evident from the literature that leukemia *per se* is not a sole indication for abortion; social and economic implications are important factors.

As to the technique of abortion during early pregnancy, Roentgen rays have the advantage that sterilization may be produced coincidentally, which may insure against future pregnancies; this also avoids hemorrhages which frequently occur after surgical manipulations. During the later stages of pregnancy, medical and surgical induction may be necessary. If, however, pregnancy is allowed to

TABLE 3.—CORD BLOOD.

	2-17-37.
Megaloblasts	1
Erythroblasts	2
Normoblasts	30
Myelocytes, neutrophils	7
Non-segmented neutrophils	5
Segmented neutrophils	36
Myelocytes, basophils	1
Basophils	4
Lymphocytes	32
Monocytes	15
Hemoglobin, %	98.0
R.B.C. (in millions)	4.7
W.B.C. (in thousands)	19.0
Platelets (in thousands)	250.0

TABLE 4.—BONE MARROW FINDINGS OF THE BABY.

	2-17-37.		2-23.	3-9.	3-17.	4-6.	4-17.	4-26.	5-4.	5-11.	5-18.	6-16.	7-20.
	Tibia.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.	Sternum.
Megaloblasts	7	1	1	..	..	6	4	8	12	3	..	2	
Erythroblasts	20	8	3	15	4	10	10	25	12	3	13	8	
Normoblasts	65	85	26	105	25	70	40	80	50	35	40	36	23
Plasma cell erythroblasts	..	..	..	..	7								
Hematogones	15	10	8	..	25	31	20	20	28	37	32	35	34
Myeloblasts	1	7	1	3	3	..	6	4	7	4	5	..	9
Myelocytes, neut.	26	30	23	24	23	12	12	17	20	15	11	14	5
Non-seg. neutrophils	33	13	25	19	23	9	30	25	15	18	31	8	11
Segmented neutrophils	11	29	33	38	30	30	20	30	15	18	10	30	25
Myelocytes, eos.	4	5	5	3	5	3	3	2	7	4	4	..	3
Eosinophils	10	8	..	8	4	6	2	1	3	1	1		
Basophils	..	1	1	..	..	..	..	..	1				
Lymphocytes	..	4	2	5	6	6	5	..	2	2	5	..	10
Large lymphocyte	..	..	..	..	1								
Monocyte	..	1											
Endothelial cells	..	2	..	..	3	..	..	..	1	..	..	3	1
Megakaryocytes	..	..	2	..	2	3	2	1	1	1	1	2	2
Total nucleated cells per c.mm. (in thous.)	34.0	60.0	65.0	132.0	126.0	352.0	266.0	360.0	344.0	248 8	202.4	182 0	68.4
Total megakaryocytes per c.mm.	..	..	..	44	176	550	376	880	383	154	242	330	110

Cod-liver oil, orange juice and ferric and ammonium citrate (sat. sol.), 0.5 dram daily, starting 3-17-37.

Ferric pyrophosphate started daily on 4-30-37.

Oleum percomorpheum started 5-20.

TABLE 5.—BLOOD COUNTS OF BABY.*

	2-17.	2-18.†	2-23.	3-2.	3-9.	3-17.	3-26.	4-6.	4-17.	4-26.	5-4.	5-7.	5-11.	5-18.	5-27.	6-16.	6-29.	7-20.
Erythroblasts . . .	1																	
Normoblasts . . .	4	2	...	...	...	...	1											
Myelocytes, neut. .	1	2	1	1	5	...	2											
Non-seg. neutrophils .	20	21	4	1	...	...	...	1	1	...	5	10	...	2	...	...	1	
Segmented neutrophils	24	47	47	36	61	22	34	22	36	65	44	35	46	35	26	45	16	28
Metamyelocyte . .	1																	
Eosinophils	...	6	5	12	7	6	7	5	3	1	6	1	2	...	3	4	5	6
Myelocytes, baso. .	...	1																
Basophils	1	2	1	2	...	...	...	...	...	1	2	1	...	...	...	1	1	
Lymphocytes . . .	46	16	12	35	9	53	39	57	47	15	24	39	44	55	44	18	66	49
Large lymphocytes .	...	...	...	1	...	4	...	...	...	...	...	...	...	...	...	...	1	3
Monocytes . . .	7	5	30	12	18	15	18	15	13	18	10	14	8	8	27	32	10	14
Hemoglobin, % . .	110.0	110.0	101.0	100.0	84.0	70.0	75.0	76.0	68.0	76.0	71.0	78.0	78.0	78.0	83.0	88.0	92.0	102.0
R.B.C. (in millions) .	4.8	5.2	4.6	4.6	4.3	4.6	4.4	3.1	3.2	3.4	3.8	3.8	4.0	4.1	4.4	4.0	5.0	5.6
W.B.C. (in thousands)	8.1	11.4	15.1	11.7	18.1	8.8	10.2	8.4	8.4	11.8	7.8	16.4	14.4	11.2	5.8	11.0	18.8	8.2
Platelets (in thousands)	260.0	230.0	120.0	100.0	180.0	280.0	260.0	90.0	260.0	210.0	310.0	240.0	380.0	280.0	230.0	200.0	250.0	270.0
Reticulocytes, % . .	4.0	2.4	...	1.0	1.0	0.5	...	5.5	1.5	2.1	2.0	2.8	2.1					
Normal coagulation and bleeding time																		
							Weights and Temperature of Baby.											
Weight	5 lbs. 13 oz.	5 lbs. 8 oz.	5 lbs. 10 oz.	5 lbs. 14 oz.	6 lbs. 1 oz.	6 lbs. 13 oz.	7 lbs. 4 oz.	9 lbs. 8 oz.	11 lbs. 1 oz.	12 lbs.	12 lbs. 8 oz.	12 lbs. 12 oz.	13 lbs.	12 lbs. 11 oz.	13 lbs. 3 oz.	13 lbs. 15 oz.	14 lbs. 2 oz.	16 lbs.
Temperature, ° F. .	99	99.1	99.5	98.9	100.6	98.6	99.1	98.6	98.8	98.8	98.8	99	99	99	98.8	98.8	98.6	98.6
			Rash		Cough Constipated						Started on iron and copper	Vomits 2 or 3 feedings daily	Vomits 2 feedings daily		Oleum percomorpheum started 5-20			

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* All blood and marrow counts taken by same person at approximately same time of day (3 P. M.).

† Baby was placed on S. M. A.

continue, irradiation therapy can be given to the patient to control the leukemic process without injury to the fetus. The usual techniques are those of Senn[31] who was the first to irradiate the spleen and Teschendorf[34] who was one of the first to introduce teleroentgenotherapy in cases which had become refractory to splenic treatment. We did not employ these techniques. Our method consists in irradiating the entire vertebral column because it includes much of the active myelopoietic system. The fields are right and left cervical, first to eighth dorsal, eighth dorsal to second lumbar, second lumbar to sacrum with the tube angled 20 to 25 degrees to the midline. The dosage is 200 to 300 r units (with backscattering), the factors being 200 kv., 25 ma., filters 0.5 mm. Cu and 1 mm. of Al, field size 15 to 20 by 10 cm., distance 50 cm. Treatments are given at intervals of 3 to 4 days. The general condition of the patient and the white blood cell count are the criteria used for determining the necessity for treatments. During pregnancy the lower fields are omitted so that direct irradiation of the fetus is avoided. Harris[12] has shown that the irradiation of the fetus may be harmful, as 1 of his cases (not leukemic) which had failed to abort after Roentgen ray exposure, but whose uterus was emptied surgically, revealed a fetus with cerebral cysts. In our case, the Roentgen ray treatment of the mother had no untoward effect on the fetus, even though she received approximately 600 r units over the lower abdomen. Assuming the depth dosage to be about 30 to 35% at 10 cm., the uterus probably did not receive more than 200 r units.

From the foregoing, it can be seen that the prevention of pregnancy by instructions in contraception should be given to leukemic women who are capable of becoming gravid. If the menstrual periods become excessive, which is a frequent complication of leukemia because of the thrombopenia, Roentgen ray castration should be considered. The amenorrhea produced by Roentgen ray sterilization is not always permanent and pregnancy may eventuate as is shown in our case and in the case described by Taussig,[32] the products of conception being normal in both instances.

In acute leukemia of both the myeloid and lymphatic types, an acute exacerbation of the leukemic process frequently follows delivery, and death rapidly ensues. Hussy[13] reports a case (acute lymphatic leukemia) that died a day after Cesarean section. The baby in this case lived and developed normally.

In chronic leukemia, delivery does not as a rule alter the leukemic process. In our case there was, however, a slight exacerbation which was easily controlled by Roentgen therapy.

With the exception of the doubtful cases reported by Cameron[6] and of a transitory leukemic phase (possibly an infectious mononucleosis), described by Russell[28] in no authentic case has leukemia been found in the offspring of leukemic mothers. However, there have been examples of leukemic offsprings from normal parents.

Pollman[26] and Lomell[21] report the blood and postmortem findings of infants 20 and 30 days old respectively who died of typical lymphatic leukemia, but whose parents were normal.

Bone Marrow and Blood Findings. The normal bone marrow differentials of adults naturally vary with thé technique and with the authors.[2,7,14,24,30,36,42] The technique which we used on the mother was merely the *insertion of a shortened lumbar tap needle (1½ inches* in length) directly through the outer plate of the sternum in the midline between the junctions of the second and third ribs. Only 0.1 cc. of marrow fluid is withdrawn. (This eliminates dilution with blood.) This large drop of marrow fluid is ejected on to a slide and a sample is taken for a total nucleated cell count, using the usual white cell pipette and 2% acetic acid (the usual white cell diluting fluid). The total white cell count (excluding the nucleated red cells) by this technique is approximately 120,000 to 180,000 in normal adults,[36] the total nucleated red cells being between 20,000 and 50,000 per c.mm. The vast majority of the nucleated red cells are normoblasts. The normal megakaryocyte count is approximately 150 per c.mm.

It must be emphasized that the total figures by this technique are only approximations. The white cell differential counts (500 cells counted) of normal sternal marrows are approximately proportioned as follows: 30% neutrophilic myelocytes, 30% non-segmented polymorphonuclears, 30% segmented polymorphonuclears and 10% other cells (myeloblasts, eosinophilic myelocytes, basophilic myelocytes, eosinophils, basophils, reticulum cells, clasmatocytes, lymphocytes and monocytes).*

Both the supravital technique and the Jenner-Giemsa stain technique were used in differentiating the blood and marrow cells in this report.

The bone marrow counts in the mother shows interesting findings. The first marrow puncture (pre-delivery) was done during a quiescent period of the leukemic process (the peripheral blood count was 34,000), the second puncture (post-delivery) was taken during an active period of the leukemic process (the peripheral blood count was 94,000) and the third during the terminal stages of leukemic process (the peripheral count was 54,400). (This patient maintained a high platelet count throughout the entire course of the disease[9] until the terminal stage was reached.) As would be expected, the marrow differentials showed a gradual but distinct "shift to the left," while the total marrow white cell count and megakaryocyte count varied according to the stage of the leukemic process and the treatment.

The blood findings in the mother previous to delivery, during delivery and after delivery could only be considered as variations due to the leukemic process, and not altered by the pregnancy.

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* This presents fewer neutrophilic myelocytes and more polymorphonuclears than is usually regarded as normal. See Custer and Krumbhaar's[11] table from which is calculated, about 65% neutrophilic myelocytes; 22% non-segmented and 4.5% segmented polymorphonuclears and 8.5% other cells.—EDITOR.

The normal bone marrow findings in infants are being determined in many clinics, using the puncture technique. Tecilazic[33] (tibial marrow) in Italy, Kato[17] and Vogel[35] (sternal marrow) in this country have shown that infant marrow varies but little from that of the adult. To obtain marrow from the tibia in our case, a Steinman pin bent at right angles[11] was inserted directly through the skin and subcutaneous tissue covering the upper third of the tibia (without an incision) and then rotated with pressure until the medullary cavity was reached. With a needle, marrow fluid was easily withdrawn. The sternal marrow was obtained in the manner as described for the mother.

The marrow findings of the baby were interesting. The total nucleated cells of the marrow gradually increased in numbers. The differentials did not vary much during the first 2 months and they corresponded quite closely to normal adult marrow findings except for the increased number of "hematogones." The megakaryocytes gradually increased. Comparison of the differentials of sternal and tibial marrow revealed little difference except for the degree of hyperplasia. After the peripheral blood elements reached the usual normal level, and this occurred during the fifth month, the marrow became less active as is shown by the lower marrow total cell count and the less active myelopoiesis and erythropoiesis.

This is one of the very few cases in which the marrow has been repeatedly examined from birth. It would appear that this newborn marrow approximates the adult marrow quite closely; the exception being the gradually increasing numbers of "hematogones," which are small cells usually having a dense nucleus surrounded by an almost imperceptible rim of cytoplasm.[17] These have been called discarded normoblastic nuclei, micromyeloblasts, precursors of the erythroblast and so forth. They are probably lymphatic cells,[7] since they are found in increased numbers in the marrows of cases of lymphatic leukemia, follicular lymphoblastoma, and infectious mononucleosis, and in smears of normal lymph nodes. However, "hematogones" are increased in the marrows of patients having untreated pernicious anemia and aregenerative anemia. As there were very few fat cells in the marrow at any time, they were not included in the differentials. Mitotic figures were no more numerous than in normal adult marrows. It was expected that distinct marrow changes either in the normoblast or erythroblast groups would be seen during the usual peripheral hemoglobin drop—the so-called "physiological anemia" period. However, no definite correlation between the marrow and the blood findings could be discovered, although there is some evidence that when the peripheral hemoglobin fell, an increase in normoblasts occurred in the marrow, while later when the hemoglobin rose, the normoblasts decrease in numbers.

The cord blood was interesting in comparison to the baby's peripheral blood findings. The baby's initial peripheral blood count was taken from the heel approximately 45 minutes after the cord blood.

The baby's initial peripheral blood findings were different from the "norms" established for premature and newborns.[15,22,23,40] (Normal newborns have about 6,000,000 red blood cells and 20,000 white blood cells during the first week of life.) Neither did these findings compare closely with the cord blood which was taken 45 minutes before. The cord blood contained more white cells, and many more normoblasts than the peripheral blood of the baby. However, dramatic peripheral blood changes occurring within very short periods of time under duress are reported in the literature.[8,39,41] Although the baby had a lower peripheral white count than is found in normal babies, the marrow responded well when necessity demanded. The infant developed a cold associated with fever during the third week of its life and a leukocytosis of 18,000, with a corresponding polynucleosis occurred. The usual normal lymphocytosis was not established until after convalescence from this cold. This baby's red cells did not vary much in numbers during the first month, and in the second month there was the usual gradual fall in hemoglobin and red cell count, while the marrow normoblast count increased. Ferric pyrophosphate (25 mg. of elemental iron[10]) was started daily at the end of the second month but no marked change in the peripheral blood nor in the marrow findings occurred in the month following this increased iron administration, but during the next month the hemoglobin rose rapidly to normal. The platelets have remained quite stable and at a normal level during the first 5 months.

In no case in the literature, where examination of the placenta has been made, were abnormal placental findings noted. Histologic examination of the placenta in this case revealed no leukemic changes.

Summary. 1. The history of a chronic myeloid leukemic patient treated by Roentgen ray, who later became pregnant, is reported. The pregnancy apparently had no influence on the leukemic process.

2. The offspring at delivery was apparently normal, and for 7 months has had a normal weight gain.

3. Repeated blood and marrow findings in the mother and offspring are presented.

We wish to acknowledge our appreciation of the coöperation of Dr. E. Friedman who delivered the patient and of Dr. Samuel Brown (Director of the Department of Roentgenology) for his constant interest.

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MACROCYTIC ANEMIA IN CANCER OF THE STOMACH, APPARENTLY DUE TO LACK OF INTRINSIC FACTOR.

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The etiology of the various types of anemia associated with cancer of the stomach has been discussed by many investigators.[6,9,10] If there is a disturbance of iron metabolism (failure of absorption or chronic hemorrhage), microcytic anemia results. This type has been attributed also to a toxic effect on the bone marrow or to hemolysis. Occasionally a macrocytic anemia has been associated with cancer of the stomach and ascribed to metastasis to the bone marrow, or to a coincidental association of pernicious anemia and cancer. The following case report and experiment illustrate another possible mechanism for the production of the macrocytic anemia in association with a neoplasm of this type.

Case 1.—Mr. J. G. K., white, farmer, aged 63, was admitted to this institute on January 30, 1934, with chief complaints of fatigability (4 months), weakness, dyspnea on slightest exertion and palpitation (present for 2 months). Pallor and a yellowish tint of the skin had been noticeable 3 weeks before admission. There had been a 5-pound weight loss. For 1 month the patient had experienced epigastric distress after meals. There was no history of glossitis, numbness or tingling of the extremities. His father died as a result of pernicious anemia, and his mother and sister from carcinoma.

Physical examination revealed an elderly male, chronically ill, but in no acute distress. The skin was pale and markedly yellowish; the scleræ icteric. Atrophy of the tongue was evident at the tip and along the margins. It was not coated. A systolic murmur was present at the apex and base. The blood pressure was 150/95. The abdomen was slightly distended, but there was no spasm, rigidity or tenderness. The biceps, triceps, knee and Achilles reflexes were equal and active. The vibratory sense was diminished over the right ankle only. Deep pain sense, as well as sense of motion and position of the toes were preserved.

Laboratory reports: The urine was essentially normal. The stools revealed no evidence of occult blood, ova, or parasites. The gastric contents on analysis, after histamine injections, contained no "free" hydrochloric acid. The icteric index was 40, and the bilirubin was 1.60 mg. per 100 cc. of blood. The red blood cell count was 1,300,000 per c.mm.; hemoglobin 32% (Sahli) (5.62 gm.). Moderate poikilocytosis was present with many oval forms. The red blood cells varied in size from 3.0 to 13.5 microns, with 44% larger than 7.5 microns.

Clinical Course. The patient was given an experimental intramuscular preparation of desiccated stomach. The reticulocytes 7 days later reached a peak of 16%. Two months later his blood count was as follows: red blood cells 4,200,000 per c.mm.; hemoglobin 87% (Sahli) (15.28 gm.) On July, 1934, 6 months after his first admission, the patient returned complaining of weakness, marked weight loss, severe epigastric distress, nausea and vomiting. The blood picture was maintained with normal limits by the daily ingestion of 20 gm. of desiccated stomach. Physical examination revealed extreme emaciation and tenderness in the epigastrium. Gastro-intestinal Roentgen rays showed linitis plastica type of deformity of the stomach, evidently carcinomatous etiology (Fig. 1).

During the patient's first admission to the hospital, daily gastric drainages were done. Approximately 1800 cc. of gastric juice were obtained over a period of 14 days. This material was divided equally into 9 parts, one of which was incubated for 3 hours at 37° C. with 200 gm. of ground beef, and fed at daily intervals to a patient with pernicious anemia in relapse (red blood cells 1,700,000 c.mm.; hemoglobin 7.8 gm. per 100 cc.). No reticulocyte response was observed for a period of 12 days. Subsequently, this same subject was given 40 gm. of desiccated stomach daily. On the fourth day after treatment was instituted, the reticulocytes increased from 0.5% to 5.8%, reached a peak of 15.5% on the eleventh day, and decreased to 4.5% on the fifteenth day (Chart I). This experiment indicates that the gastric juice obtained from the patient with linitis plastica apparently did not contain the "intrinsic factor," as do normal secretions.

Discussion. Castle,[1–4] by several ingenious experiments, proved that normal gastric juice when incubated with beef steak was effective in producing a remission in pernicious anemia. He postulated that the stomach secretions of normal individuals contained a factor (intrinsic) which was necessary for the maturation of red blood cells, and this substance was absent in the gastric contents of persons with pernicious anemia; hence the development of the macrocytic anemia. In a former paper,[5] it was demonstrated that the

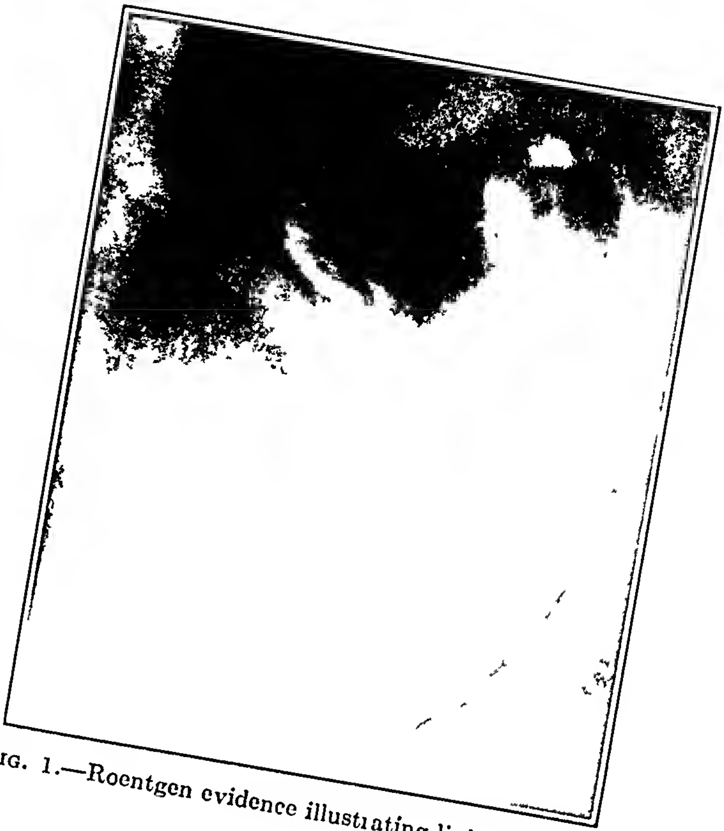

Fig. 1.—Roentgen evidence illustrating linitis plastica.

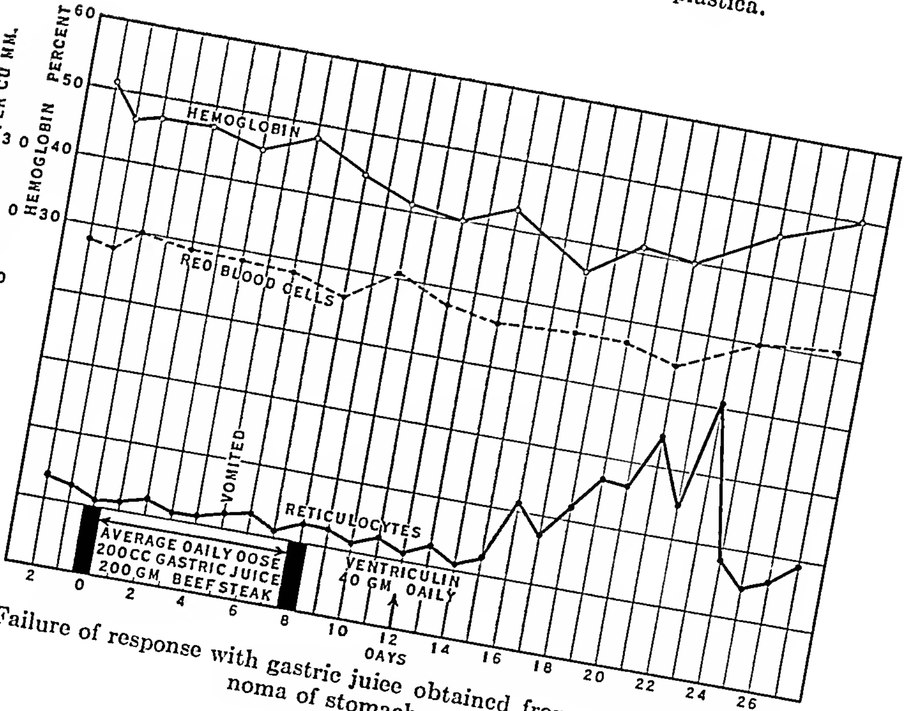

Chart I.—Failure of response with gastric juice obtained from patient with carcinoma of stomach.

defect in gastric secretion in pernicious anemia was quantitative rather than qualitative. The intrinsic factor was present in the gastric juice but in reduced amounts, and the peripheral red blood cell count was proportional to the decreased gastric juice volume.

In the experiment just described, it appears that the intrinsic factor is absent, supposedly as a result of the invasion of the gastric mucosa by the widespread carcinoma. Since the intrinsic factor is a necessary substance for normal hematopoiesis, when it is absent as in this case, a macrocytic anemia similar to that noted in pernicious anemia will develop. With these facts at hand, one must speculate as to why this patient was able to produce any mature red blood cells. It had been previously demonstrated that the normal liver contains a hematopoictic substance which is not an integral part of the hepatic parenchyma, but stored there and released to the body as needed.[7] Following gastrectomy in humans, the macrocytic anemia which may result, does not appear for at least 2 years. It is suggested therefore, that the body has stored a sufficient amount of erythrogenic material to maintain a normal red cell production for at least this period. Goodman, Geiger and Claiborn[8] showed that subsequent to the removal of the stomachs of pigs, the hematopoietic-producing substance of the liver was gradually diminished.

In the individual with gastric carcinoma, a hematopoietic "gastrectomy" has been produced by the malignancy. The normal stomach functions have been destroyed by the cancer with a failure of secretion of the intrinsic factor. Consequently, the normal rate of red cell formation will continue until the storage of the hematopoietic substance in the liver is depleted; then, with the failure to supply an adequate amount of this material for erythrogenesis, the production of the mature red cells will fall gradually.

The possibility of the association of gastric carcinoma and pernicious anemia cannot be denied in this case, although there is suggestive evidence which indicates that this relationship did not exist. For example, in pernicious anemia, the "intrinsic" factor may be present in reduced amounts in the gastric contents, whereas in this instance it was completely absent, probably as a result of gastric dysfunction caused by the malignancy. Clinically, the patient had no findings suggestive of pernicious anemia, other than the macrocytic anemia. There was no positive evidence of central nervous system degeneration which has been observed in 90% of the cases of Addison-Biermer type of anemia and glossitis was absent.

Summary. A macrocytic anemia may be produced by several combinations of factors. It is generally accepted that the interaction of an extrinsic factor in food and an intrinsic factor produces a substance necessary for the normal development of red blood cells. The product formed is presumably absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed. If there is a disturbance of any of the factors which are involved in this mechanism, a macrocytic anemia will result. In this case of carcinoma of the stomach, the macrocytic anemia responded to anti-anemia therapy, and his gastric juice did not contain the intrinsic factor. Other than the anemia, he had no clinical findings supporting a diagnosis of pernicious anemia. It seems, therefore, that his macrocytic anemia resulted from the failure of the cancerous stomach tissue to produce the necessary intrinsic factor, or from the destruction of the latter by the malignant tissue or its toxin.

Conclusions. 1. A case of cancer of the stomach with an associated macrocytic anemia is described.

2. The anemia responded readily to desiccated stomach therapy.

3. The gastric contents obtained from the cancerous stomach did not contain the intrinsic factor.

4. The macrocytic anemia associated with cancer of the stomach may result from the failure of the "intrinsic" factor to be produced by the malignant tissue.

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THE CHARACTER OF THE LEUKOCYTIC RESPONSE TO TUBERCULIN IN SENSITIZED CALVES.

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In a previous experiment[1] we attempted to obtain experimentally in rabbits a leukocytic response comparable to the so-called leukemoid reaction occasionally associated with tuberculosis in human beings. In rabbits infected with tubercle bacilli we observed that following the injection of tuberculin there occurred a striking elevation of the leukocyte count with a marked shift to left of the cells of the granulocytic series. The changes in the peripheral blood and in the bone marrow after tuberculin was injected resembled the condition in human beings which Krumbhaar has designated as "leukemoid." Since the rabbit is recognized as being extremely responsive to most of the hematopoietic stimuli it seemed desirable to ascertain if similar reactions could be induced in animals other than the rabbit. As part of another experiment there were available a number of tuberculous bovine animals, and these were utilized to determine if the so-called leukemoid response would occur following the injection of tuberculin.

Methods. The animals consisted of 8 apparently healthy calves which were approximately 3 months of age. These animals had been tested previously with the intradermic tuberculin test;* and none of the animals reacted positively. The animals were divided into four groups of 2 each and each group was placed in a separate pen. An adequate ration consisting of alfalfa hay, ground grain, skim milk, potassium iodide, and cod-liver oil was supplied. Six of the animals received subcutaneously 2 cc. of a saline suspension of a virulent strain of bovine tubercle bacilli. For control purposes 2 of the animals were not injected with tubercle bacilli.

The blood was examined on 3 successive days prior to receiving the tubercle bacilli and once every week for 8 weeks after injection. After the last of the weekly blood examinations, each of the calves was injected intracutaneously in each caudal fold with 0.2 cc. of standard intradermic tuberculin (equivalent to 0.05 gm. of Old Tuberculin). After the intracutaneous injection of tuberculin the blood was examined on each of the next 3 days. The blood examinations were then discontinued for 5 days and resumed on the sixth day.

On the seventh day following the intracutaneous injection of tuberculin and approximately 9 weeks after the animals had been infected with tubercle bacilli, each of the calves was injected subcutaneously with a solution of tuberculin equivalent to 2 gm. of Old Tuberculin. In addition to the observations on the blood, the thermic reaction to the tuberculin was also recorded. The first postinjection temperature was taken 6 hours after the tuberculin was given and temperature readings were continued at intervals of 2 hours for 22 hours. The temperature readings were then discontinued for 10 hours after which 4 more temperatures were taken at intervals of from 4 to 14 hours (Fig. 1).

After the completion of the experiment the animals were killed and submitted to postmortem examination. Marked and in some instances extensive lesions of tuberculosis were present in each of the 6 animals which had been injected with tubercle bacilli. The area of inoculation showed caseocalcareous lesions with involvement of the regional lymph nodes, the subscapular and axillary nodes being most often affected. Slight or early lesions of tuberculosis were demonstrated in the lungs of only 2 of the animals although the bronchial and mediastinal lymph nodes were involved in 4. In 3 instances lesions of tuberculosis were present in the spleen but in only 1 instance were lesions found in the liver. No lesions of tuberculosis were found in the control or non-infected calves.

Quantitative and qualitative studies of the leukocytes obtained from the peripheral blood were made. To detect anemia, parallel readings on red cell counts and hemoglobin estimations were made.

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* The tuberculin used was kindly furnished by the Bureau of Animal Industry of the U. S. Department of Agriculture.

The blood specimens were obtained from a freely flowing marginal ear vein and standard pipets were used for the dilution of the blood The amount of hemoglobin in grams per 100 cc. of blood was determined by the use of the photoelectric hemoglobinometer described by Sanford and Sheard.[6] The blood smears were stained according to the May-Grünwald-Giemsa method. For differential counts, 200 cells were counted routinely and the absolute number of the different varieties per cubic millimeter of blood was calculated.

Changes in the Peripheral Blood. The blood picture before the infection and prior to the injection of tuberculin was noted mainly for the purpose of establishing a base line for the detection of qualitative and quantitative changes that might occur after tuberculin was administered.

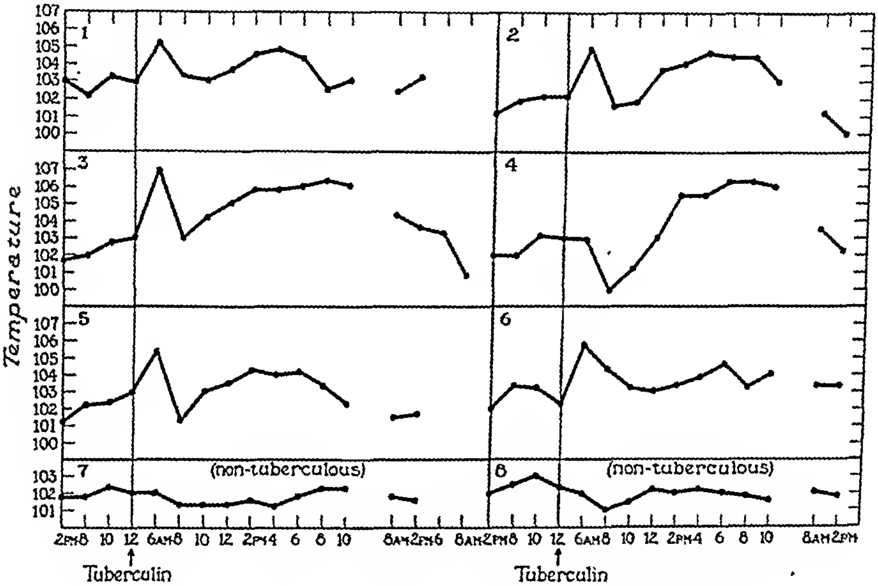

FIG. 1.—Thermic reactions following subcutaneous injection of tuberculin into tuberculous calves; each calf received tuberculin equivalent to 2 gm. of Old Tuberculin.

Changes Before Infection. Our data concerning the normal values for erythrocytes, hemoglobin and leukocytes were essentially in agreement with the data given for cattle by Kohanawa[3] and by Wirth.[9] The average value for erythrocytes before tubercle bacilli were injected, for the 8 animals was between 5 and 7 millions. Miller[5] found the erythrocyte values for presumably normal animals of comparable age to be 6,080,000 to 8,648,000 per c.mm. of blood. The average value for hemoglobin in 100 cc. of blood in our animals was 11.45 gm., while Schmidt[7] gives the mean value between 9 to 13.6 gm. The normal leukocyte count for calves is according to Wirth between 12,000 and 15,000 per c.mm. and according to Miller the mean value is 11,332; the 8 animals in our series showed an average of 3 successive days of 10,024. According to Wirth, the majority of the white cells are lymphocytes, and the average differential count is as follows: lymphocytes, 50%; neutrophils, 30%; eosinophils, 6%; basophils, 0.1%; monocytes, 5%. Hofferber[2] stated that even in healthy animals the neutrophils varied from 3 to 65%.

Changes After Infection. During the progress of the disease the blood picture of the tuberculous animals varied considerably (Fig. 2). There was a considerable fluctuation of the leukocyte count and an absolute increase in lymphocytes. There was also a slight increase in the number of monocytes. Occasionally, the presence of metamyelocytes was also noted. Hofferber stated that the presence of tuberculosis in cattle is indicated by the occurrence of a distinct anemia due to a decrease in the number of erythrocytes with a reduction of the hemoglobin content. We also observed

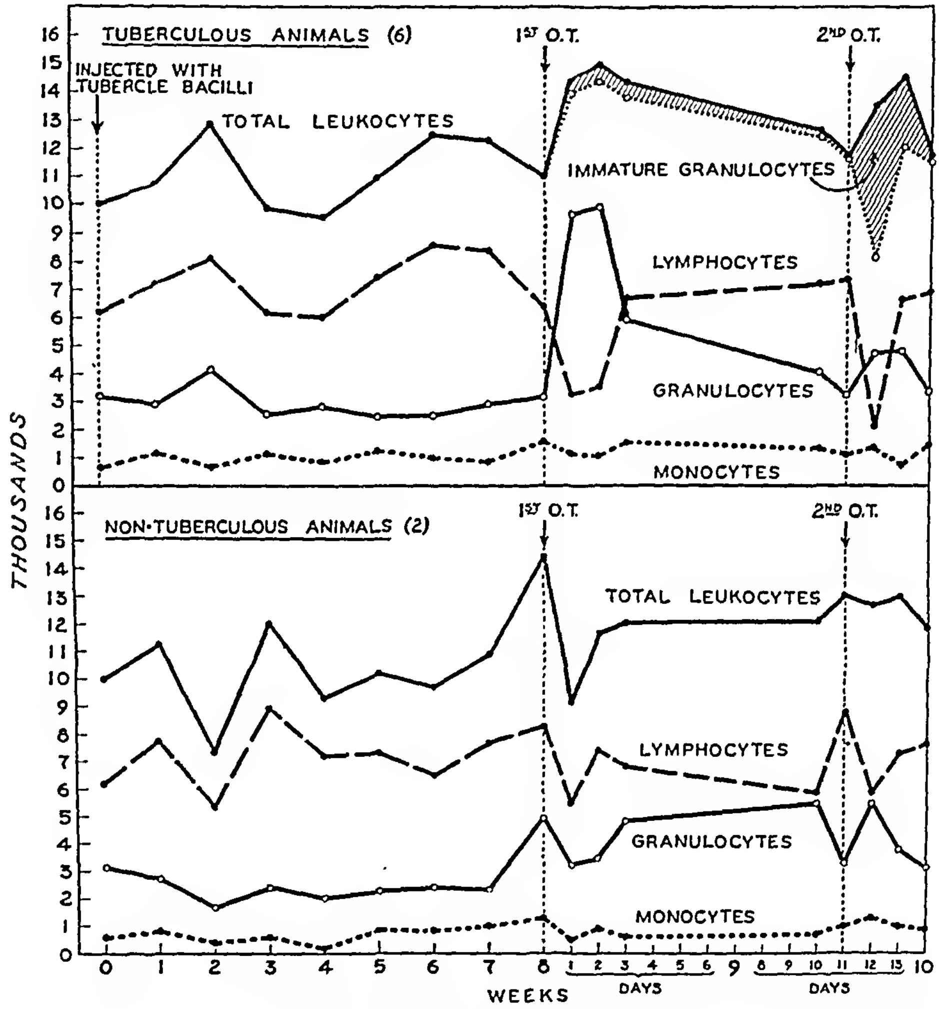

FIG. 2.—The total number of leukocytes and the absolute number of monocytes. granulocytes, lymphocytes and immature myeloid cells in thousands per c.mm. of blood.

some reduction in the value of hemoglobin which was associated with a decrease in the erythrocyte count. The average value for hemoglobin for the 6 animals at the beginning of the experiment was 11.45 gm. per 100 cc. of blood and the average value for the 6 animals 8 weeks after the infection was introduced was 8.93 gm. Similarly, the red cell count dropped from an average for the 6 calves of 5,600,000 per c.mm. of blood when the experiment began to an average value for the tuberculous animals of 4,800,000 at the end of the eighth week. In the 2 control calves no quantitative changes were noted in the hemoglobin values and the red cell counts.

Changes After First or Intracutaneous Injection of Tuberculin. After the first or intracutaneous injection of tuberculin there occurred within 24 to 72 hours an increase in the total number of leukocytes which was accounted for largely by an excessive number of neutrophils (Fig. 2). At the same time the lymphocytes showed a definite tendency to diminish in number. The white cell count in the 2 control animals also showed some fluctuations during the first 3 days after the injection of tuberculin but the disproportional increase of the myeloid cells seen in the sensitized calves did not occur (Fig. 2).

Changes After Second Injection of Tuberculin. Twenty-four to 48 hours after the second injection of tuberculin the total leukocyte count of the sensitized calves showed a moderate rise which was characterized by a definite stimulation of the cells of the myeloid series. The increase in the leukocyte counts represented an absolute increase in the number of neutrophils with a marked shift to the left. Promyelocytes, myelocytes and metamyelocytes were readily demonstrable. All 3 varieties of the polymorphonuclear cells, the neutrophilic, the eosinophilic and the basophilic, were increased. The number of monocytes also showed an increase but as compared to the rise in the number of polymorphonuclear cells the increase was not so striking. The lymphocytes showed a definite tendency to diminish in number following the injection of tuberculin. Abnormal cells which resembled Türck cells and plasma cells, were also noted frequently. Studies of the blood of the 2 control animals failed to show comparable changes.

The morphologic characteristics of the leukocytes of the calves may be described briefly as follows: The individual cells of the entire myeloid series in cattle are normally of considerable size. The earliest forms of the myeloid series, such as myeloblasts and leukoblasts, were not seen. The promyelocytes were characterized by a blue cytoplasm and a pinkish perinuclear zone, showing signs of acidophilic metamorphosis. The chromatin exhibited certain degrees of condensation but still retained a delicate structure. The myelocytes had a definitely pink cytoplasm containing indistinctly staining large true neutrophilic granules. The round, oval or slightly indented nucleus of these cells contained well-defined chromatin and parachromatin, which gave a somewhat coarse appearance to the pattern of the nucleus. The metamyelocytes had definitely indented nuclei. The chromatin of the metamyelocytes was condensed and was similar in pattern to that of a mature granulocyte. There were numerous transitional forms from the metamyelocyte to the mature form of granulocyte. The mature neutrophils were similar morphologically to those of human beings, but differed from the latter in having very faintly stained, indistinct granules and being considerably larger in size. The eosinophils had a two- or a three-lobed nucleus and numerous large granules were present in the rather abundant cytoplasm which had a strong affinity for the acid stain. The eosinophilic myelocytes and metamyelocytes were similar to those of human beings. The basophils had a two-lobed nucleus and the cytoplasm was studded with a large number of distinct deeply staining granules.

The lymphocytes varied in size and shape. The nuclei were round and contained coarsely condensed chromatin masses. The cytoplasm consisted of a narrow rim of variable width which stained blue and had a ground-glass appearance. It contained a few coarse azure granules. Occasionally, because of a deep blue color of the cytoplasm and a markedly coarse pattern of the chromatin, some of the lymphocytes resembled plasma cells. There also occurred cells with deeply staining cytoplasm in which the nuclear structure revealed a fine distribution of chromatin. These cells resembled the so-called irritation cells of Türck. The monocytes were characterized by a light blue, foamy cytoplasm containing fine azure granules. The nuclei of the monocytes were deeply indented or slightly convoluted and had a fine nuclear pattern.

Comment. We have found but few reports in the literature of studies of the changes in the blood that occur following the administration of tuberculin to tuberculous animals. Scholz,[8] in 1912, observed the hematologic changes in tuberculous calves, rabbits and guinea-pigs following the injection of old tuberculin and he noted an increase in the number of leukocytes and a decrease in the number of erythrocytes. Wirth also referred to the observations of several authors who found that the injection of tuberculin into tuberculous animals provoked an increase in the number of leukocytes while very large doses of tuberculin resulted in leukopenia. Recently, Hofferber studied the blood of tuberculous cattle, but he did not include the reaction to tuberculin in his investigation.

In our work we have found that the injection of tuberculin into sensitized rabbits institutes a striking rise in the total leukocyte count. These changes represent an overstimulation of myeloid tissue. In the present study, while the total leukocyte count did not exhibit the striking rise noted in sensitized rabbits, the qualitative hematologic changes were essentially comparable. Following the injection of tuberculin into sensitized calves there occurred an absolute and relative increase of neutrophils with a definite shift to the left which was reversible. The lymphocytes had a tendency to diminish during the period of the reaction to tuberculin while during the development of the tuberculous infection the lymphocytes definitely outnumbered the myeloid cells. It was also noted that the administration of larger doses of tuberculin was followed by the appearance of immature cells markedly in excess of the number that occurred following the first injection of tuberculin.

The failure of tuberculin to provoke in the sensitized calves an increase in the total number of leukocytes of such spectacular proportion as we had observed previously in rabbits could not have been due to an inadequate sensitivity to tuberculin. That a marked state of sensitivity was present is evident from the profound systemic disturbance that followed the injection of tuberculin and from the marked increase in the temperatures that were recorded for the respective animals. The explanation for the failure of the leukocyte to occur in large numbers in the calves must be sought in the hemopoietic propensities of the myeloid tissues. Evidently the bone marrow of most cattle is incapable of a sudden, excessively large production of neutrophils, while the converse is true in the rabbit. Yamamoto[10] has shown that the bone marrow of rabbits under normal conditions is usually in a vigorous state of granulocytic activity. These immature cells are predominantly premyelocytic in character. Such an excess of immature cells, although normal for the rabbit, if found in other species would be strongly suggestive of a severe reaction to an infection or a leukemia of the myeloid type. The marrow of the sensitized bovine animal does, however, respond qualitatively to the stimulus of tuberculin and is capable of producing and releasing into the peripheral circulation many different varieties of immature myeloid cells. Although, in the bovine animal such early myeloid cells as leukoblasts and promyelocytes were relatively infrequent, their occurrence together with the regular appearance of myelocytes and metamyelocytes constitutes definite evidence of the same trend toward granulocytic stimulation as was true in the rabbits. In other words, the differences in the myeloid reactions of the two species of animals is essentially one of degree.

Conclusions. We feel, therefore, that the present observations justify the following conclusions: 1, tuberculin administered to sensitized calves provokes a leukocytic reaction comparable qualitatively to that which has been described previously in sensitized rabbits, and 2, the character of the "leukemoid" reaction resembles the condition in human beings which Krumbhaar[4] designated by this term.

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THE ETIOLOGIC RELATION OF THE EOSINOPHIL TO THE GORDON PHENOMENON IN HODGKIN'S DISEASE.[*]

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In 1932, Gordon[5a] reported that the tissues of Hodgkin's disease contain an apparently specific pathogenic agent. He had found that the injection of lymph node suspensions into the brains of rabbits induces a paralysis similar to that seen in the encephalitis caused by herpes or vaccinia virus. Subsequent investigation of this phenomenon has led to considerable controversy regarding both its nature and its significance.

Numerous studies have been made of the use of the Gordon test as a practical diagnostic procedure.[1,4,5b,11a,b] It has been shown to be positive in about 75% of all cases of Hodgkin's disease and almost invariably negative in other lymph node malignancy.[9] A few false positives have been noted, however,[1,8,9] and final judgment of the test has therefore awaited the determination of the character of the pathogenic agent involved. Thus there seems at present neither unanimity of opinion nor a theory entirely consistent with the facts.

Gordon's early belief that he was dealing with a filterable virus has not received support from recent studies.[1,6,10] That the pathogenic agent is ultramicroscopic in size and that the disease which it produces in animals bears certain marks of an infectious process cannot be disputed. On the other hand, its cultivation *in vitro* and its serial transmission from animal to animal have not been accomplished.[1,10] Moreover, animals that recover from an initial attack of paralysis are none the less susceptible to a second injection of pathogenic substance,[1,10,11a] whereas most virus infections confer a permanent immunity after recovery.

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[*] Read in part before the American Society for Clinical Investigation, May 3, 1937.

Another hypothesis was suggested by the work of Friedemann and Elkeles,[3] who showed that a paralysis indistinguishable from Gordon's may be produced with extracts of normal human bone marrow or leukocytes. The pathogenic agent present in these tissues might therefore be identical with that found in Hodgkin's disease, both being derived from the white blood cells.[2] The similarity of the biologic properties of the agents derived from these various sources has led to the complete acceptance of this idea by 2 recent investigators.[6] On the other hand, it is puzzling to find the pathogenic substance lacking from so many tissues containing large numbers of leukocytes. Thus, it is absent from some specimens of bone marrow and of pus.[5c] Moreover, evidence has not yet been brought forth to indicate that the lymph nodes of Hodgkin's disease which give a negative Gordon test differ in cellular structure or in their content of leukocytes from those which give a positive test.[1,11a]

An explanation for this discrepancy lies in the possibility that a particular type of white blood cell, rather than all types collectively, might be the determining factor. Observations made during the past year, and now to be reported in this paper, support this conception and indicate further that the responsible cell is, specifically, the eosinophil.

The evidence for a relation between eosinophil and pathogenic agent as they occur in the tissues of Hodgkin's disease is first considered.

Method. In the performance of the Gordon test the technique originally prescribed[5a] has been followed. The lymph node to be examined is minced in a mortar and suspended in 9 parts of beef infusion broth. The preparation is now transferred to the refrigerator where it remains for a week or more. This preliminary period of storage is essential because autolysis is apparently concerned in the production of pathogenic substance.[5c] After maceration has been allowed to take place for 1 to 2 weeks, injections are made into the occipital lobe of the brains of rabbits of guinea pigs. In positive cases the animals develop ataxia and paralysis after an incubation period of 2 to 14 days.

During the past year material from all lymph nodes coming under observation has been subjected to the Gordon test according to this method. It is important to point out that each preparation has been tested not only after the customary 1 to 2 weeks of refrigeration but again several months later.

Results. Eleven lymph nodes showing the histologic changes of Hodgkin's disease have been tested (Table 1). The result has been judged positive only when at least 2 animals have developed the typical paralysis, negative only if all of 2 or more animals have remained normal after injection. In 5 instances the test was positive, in 6 it was negative. In 3 of the former the test performed at 2 weeks was negative, but the later test was positive (Nos. 346, 368, 373 B, Table 1). Thus although the minimum period of storage necessary to the fullest yield of pathogenic substance cannot be estimated with accuracy, it would appear to be longer than the 2 weeks heretofore in general use.

Early in the present investigation it had been impossible to correlate any feature of the histologic structure of the involved lymph nodes with the presence of the pathogenic substance; but when 3 late positive results appeared reëxamination of the pathologic sections was undertaken. It was then found that when the Gordon test had been positive eosinophils were invariably present, and that in each case their number roughly paralleled the rapidity of development of pathogenic agent. Thus, the 2 lymph nodes which gave a positive result at 10 days contained many more eosinophils than did the 3 late positive cases. On the other hand, when the Gordon test was negative eosinophils were remarkably rare or absent.

TABLE 1.—RESULTS OF TEST IN HODGKIN'S DISEASE.

No.	Result of initial test after storage of 10 to 14 days.	Result of second test performed after length of storage indicated.	
346	0	+	3 mos.
347	0	0	3 "
353	+	—	—
358	0	0	7 "
368	0	+	5 "
371	0	0	4 "
373 A	0	0	5 "
373 B	0	+	5 "
375	0	0	5 "
376	+	+	4 "
377	0	0	3 "
385	0	0	2 "

One case of particular interest was that of a boy from whom a piece of spleen and a cervical lymph node were removed at postmortem examination. Suspensions were prepared from each specimen for the Gordon test (Nos. 373 A and B, Table 1). After 5 months the lymph node gave a positive result while the spleen remained negative. Histologically, both tissues showed extensive replacement by typical Hodgkin's granuloma, but the lymph node contained a moderate number of eosinophils and the spleen almost none.

In the control series of 12 cases (Table 2), the Gordon test was negative throughout and eosinophils were not found in any of the corresponding sections. It would appear, therefore, that the eosinophil itself might well be responsible for the Gordon phenomenon.*

In order to test the significance of this correlation, experiments were carried out in a comparable manner with suspensions of normal leukocytes.

By differential centrifugalization the leukocytic cream was separated from the oxalated whole venous blood of normal and variously diseased individuals, some of whom had a high degree of eosinophilia. Differential white blood cell counts were made on smears taken directly from the leukocytic cream, which was then suspended in 2 cc. of beef infusion broth. It was now possible to determine the number of each type of leukocyte per c.mm. The preparations were heated to 56° C. for 1 to $1\frac{1}{2}$ hours in order to insure sterility. It has been shown that a temperature of 56° C. for 24 hours will not injure the pathogenic agent.[7] Supernatant fluid from each suspension (0.2 cc.) was then injected into the occipital lobe of a guinea pig (Table 3). Any suspension containing 2000 eosinophils per c.mm. or more produced a paralysis indistinguishable from that

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* A study of the Gordon phenomenon in a variety of non-Hodgkin's cases of eosinophilia is obviously indicated but we have not been able to undertake this at the present time.

TABLE 2.—GORDON TEST IN CONTROL LYMPH NODES.

No.	Diagnosis.	Duration of storage to last testing.	Result.
348	Branch. cyst	16 days	0
349	Carcinoma	10 wks.	0
350	Sarcoma	10 days	0
352	Tuberculosis	15 "	0
355	Chronic inflammation	10 wks.	0
357	Lymphocytoma	5 "	0
359	Sarcoid	2 mos.	0
362	Chronic inflammation	8 "	0
364	Lymphatic leukemia	13 days	0
365	Lymphatic leukemia	3 wks.	0
370	Carcinoma	3 "	0
372	Sarcoma	18 days	0

TABLE 3.—GORDON TEST OF LEUKOCYTIC CREAM.

No.	Diagnosis.	Total white blood cells of suspension per c.mm.	Polymorphonuclear neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Result.
1	Normal	17,900	6,802	9,129	1969	0	0	Neg.
2	Carcinoma	45,000	38,872	4,972	900	0	0	Neg.
3	Normal	22,500	14,850	5,625	1800	225	0	Neg.
4	Normal	14,000	7,560	5,180	980	280	0	Neg.
5	Pneumonia	31,600	24,964	4.108	1896	316	0	Neg.
6	Normal	12,000	7,080	3,600	720	360	240	Neg.
7	Heart disease	28,600	23,452	3,146	1430	572	0	Neg.
8	Normal	17,000	8,500	7,310	510	680	0	Neg.
9	Normal	32,750	18,312	10,791	2616	981	0	Neg.
10	Pulmonary tbc.	12,300	7.257	2,214	738	2,091	0	+
11	Rheumatic fever	26,300	13,000	10,257	789	2,104	0	+
12	Trichiniasis	23,000	10,810	8,280	920	2,990	0	+
13	Asthma	29,250	20,400	4,380	292	3,796	0	+
14	Asthma	29,500	17,405	5,900	295	5,900	0	+
15	Trichiniasis	45,000	17,550	15,300	900	10,800	0	+

seen in the positive Gordon test, while the numbers of any other type of white blood cell appeared to exert no such influence.

From Table 3 it appears that the critical number of eosinophils lies between 1000 and 2000 per c.mm. of suspension. It may be assumed that about the same number is necessary to the potency of lymph node preparations. A first approximation to the minimum number of eosinophils which should therefore be present in an average oil-immersion field of the microscopic sections from such a lymph node may be calculated as follows:

$$\text{Eo} = \frac{(1500 \pm 500) \times \text{area of oil field} \times \text{thickness of section}}{\text{Titer of suspension (expressed as fraction)}}$$

With the microscope used in the present work this becomes

$$\text{Eo} = \frac{(1500 \pm 500) \times 0.017\ \text{mm}^2 \times 0.006\ \text{mm.}}{1/10} = 1.5 \pm 0.5$$

Actual eosinophil counts were made on the sections from all cases of Hodgkin's disease. The mean number of these cells per oil field was found to be less than 1 in each case in which the Gordon test had been negative, 1.5 to 3 in each case in which the test had been positive only after several months, and from 10 to 20 in those cases which had given a positive result at 2 weeks. These findings are evidence for the validity of the above formula.

Comment. The data which have been presented show that development of pathogenic substance in the lymph nodes of Hodgkin's disease or in normal myeloid tissue takes place only in the presence of a certain critical number of eosinophils and appears to be independent of all other types of leukocytes. If this is confirmed by future investigation the origin as well as the identity of the agents of Gordon and Friedemann would seem to be clearly established.

It follows that the Gordon test is of little value as a practical diagnostic measure since it might be positive in any condition in which the tissues are infiltrated by eosinophils. Thus it has been shown to be positive in a lymph node involved by metastatic carcinoma with eosinophilia.[8]

The suggestion has been made that if the agent found in Hodgkin's disease were proved to be identical with that found in bone-marrow, support would be lent to Medlar's hypothesis that Hodgkin's disease is a megakaryocytoma, or bone-marrow tumor. Since the agent is not specific to the marrow but to a cell found in numerous other organs and tissues such support disappears.

The exact nature of the pathogenic agent remains unknown. It appears to develop from the tissues of primates only[10] and it is therefore similar to, and possibly identical with, the Charcot-Leyden crystal, which has long been looked upon as a derivative of the primate eosinophil.

In conclusion, it would appear that the human eosinophil is distinguished among leukocytes in giving origin to the peculiar substance which was first demonstrated by Gordon in the lesions of Hodgkin's disease. It is to be hoped that future studies of this substance may throw light upon the functions of the eosinophil itself.

Summary. 1. In a series of 11 cases of Hodgkin's disease the Gordon test has been positive only when eosinophils could be found in the corresponding microscopic sections. The number of these cells was found to parallel the rapidity of development of the pathogenic substance upon which the positive test-depends.

2. The pathogenic agent described by Friedemann and Elkeles in myeloid tissues has been shown to be present only in those suspensions of leukocytic cream that contain more than a certain number of eosinophils.

3. Gordon's agent and Friedemann's agent would both therefore appear to be derived from the eosinophil and consequently are probably identical.

4. The Gordon test is positive in Hodgkin's disease only by virtue of the presence of eosinophils in the lesions of this disorder.

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A STUDY OF TUBERCULOUS SPLENOMEGALY AND SPLENOGENIC CONTROLLING OF THE CELL EMISSION FROM THE BONE MARROW.

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BY tuberculous splenomegaly is understood that clinical picture which is characterized by an enlarged tuberculous spleen, without or with only slight tuberculosis in other organs. Anomalies of different kinds as a rule are present in the peripheral blood. The term "primary tuberculosis of the spleen" is inadequate and misleading, as tuberculosis of the spleen must always be secondary. Most modern writers now agree in calling the condition tuberculous splenomegaly.

The disease is comparatively rare; from the whole world we have reports of only about 80 cases. It may therefore be of some interest

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* Aided by a grant from The Lady Tata Memorial Trust

to give a survey of its features, both because 4 new cases have been observed and because the changes in the blood picture throw light on the influence of the spleen on the bone-marrow function.

The common tuberculosis of the spleen seen in cases of generalized tuberculosis will not be mentioned in this report. According to Winternitz,[41] 67% of 400 cases of tuberculosis in children, and 19% of more than 800 cases in adults, showed tuberculosis of the spleen. Klotz[17] found it in 69 of 172 postmortems in tuberculosis; Lubarsch[22] in 41.5% of 718 cases of chronic tuberculosis and in every case of generalized and miliary tuberculosis. Not one of these cases, however, showed a splenomegaly caused by tuberculosis.

Case Reports. CASE 1.—A woman, aged 68, entered the hospital on May 6, 1935 (Kommunehosp. VII Dept. Jour. 596/1935). She had been suffering from myxedema since 1919. Treated with thyreoidine. For the past 2 months complaints of lassitude and giddiness. Her physician prescribed iron for her anemia (hemoglobin 50%). The condition became aggravated and she was admitted to the hospital.

Physical examination on admission gave the following findings: Height, 152 cm.; weight, 68 kg. Markedly anemic with slight jaundice; tongue smooth with papillary atrophy; no palpable enlargement of liver or spleen. The chief complaints were want of appetite and lassitude. While in the hospital there was now and then slight fever (38° C.).

Laboratory findings: Stools contained no blood; Wassermann reaction negative; test meal (40 min.): achylia; urine, negative.

TABLE 1.—BLOOD FINDINGS IN CASE 1.

Date	5/7	5/9	5/29	6/14	6/29	7/12	7/19
Hemoglobin, %	57.0	58.0	45.0	41.0	41.0	53.0	62.0
Erythrocytes (mill./c.mm.)	2.3	2.4	2.1	1.8	1.6	2.0	2.78
Color index	1.2	1.2	1.1	1.1	1.1	1.3	1.12
Icterus index	11.0	11.0	11.0	8.0	9.0	6.0	9.0
Sedimentation rate (mm./1h.)	....	126					
Leukocytes (thous./c.mm.)	2.3	2.0	2.4				
Platelets (thous./c.mm.)	....	233.0	115.0				
				↑ Treatment with "Pylorin"		↑ Treatment with liver	

Pernicious anemia was diagnosed and the patient treated with liver extracts, hydrolysated casein and gastric preparation (Pylorin, Leo) without effect. Daily determinations of the percentage of reticulocytes showed no rises beyond 2 to 3%, only once 3.9% was recorded.

Death occurred after sudden chills with high temperature.

Autopsy (performed by the author the following day; 521/1935): Pale skin. Slight papillary atrophy of the *tongue* and some hypoplasia of the lymphatic tissue at the base of the tongue. *Pleural cavities*, negative. *Lungs*, heavy, large, very much congested, edematous. No pneumonia. The *lymph nodes* of the hilus were of walnut-size, and very firm. The cut surface was light yellow. No necroses or abscesses. The *heart* was negative. The *liver* weighed 1560 gm., of usual size and form, but firmer than usual and somewhat congested. The *pancreas, kidneys* and *urine bladder* were negative. The *spleen* weighed 460 gm. The capsule was somewhat thickened, with scattered hyaloserositic spots. The cut surface was in one color, bright red, the pattern obscured. The pulp was firm, fragile but not dense. In the pulp were two yellowish-white nodules of pea-size. The femoral *bone marrow* was deep red, mushy.

Microscopic Examinations. Spleen: Marked hyperplasia of the red pulp with numerous reticulum cells and marked congestion. Lymphatic follicles were few, of the usual type, mostly very small. Numerous scattered, partly confluent small nodules built up of epithelioid cells. In these nodules several typical Langhans' giant cells. Little or no necrosis. Connective tissue was not increased. *Liver:* Slight vacuolar degeneration of parenchyma. A few small typical nodules of epithelioid cells found in the periportal spaces. *Lymph node from hilus:* Confluent areas of epithelioid cells with Langhans' giant cells. Large areas of necrosis with scattered foci of calcification. *Bone marrow* (femur): Marked hyperplasia with only very few fat cells. Myelocytes, promyelocytes and normoblasts dominating. No abnormal cells. No mitoses. Considering the age of the patient, the hyperplasia is outstanding.

In Ziehl-Neelsen-stained slides of liver and spleen no tubercle bacilli were found.

Diagnoses. Tuberculous splenomegaly. Miliary tuberculosis of the spleen and liver. Tuberculosis of pulmonary lymph nodes. Edema and congestion of lungs. Marked hyperplasia of bone marrow. Anemia.

Case 2.—A woman, aged 44, had since 1922 been slightly jaundiced, after a onset with high temperature of 2 weeks' duration. Since then loss of weight (35 kg.) and weakness. Hospitalization had been necessitated several times because of hematemeses; on one occasion hemorrhagic purpura was noticed. Since 1932, when she again suffered from hematemesis, purpura and enlargement of the spleen and liver, the patient has been out of work. A progressing anemia and ascites now developed and she entered the hospital on July 1 (Finsen Institute, Surg. Dept., 10604/1936).

Physical Examination. A fairly well-nourished woman with slightly icteric and brown pigmented skin. After draining a considerable ascites (6000 cc.), the enlarged liver and spleen were palpated. The rest of the physical examination was negative. For blood examinations see Table 2.

The fragility of the red cells was normal (lower limit; 0.30% and upper limit, 0.42% of saline). Tests of the liver function with galactose and examination for quinine-resistant lipases in serum showed normal findings. Wassermann reaction was negative, Mantoux reaction with 0.01 mg. of tuberculin: after 24 hours slightly positive; after 48 hours negative. Blood pressure (systolic) was 130 mm. Hg. Roentgen ray examinations of the lungs showed no signs of tuberculosis.

Table 2.—Blood Findings in Case 2.

Date	4/25/35	7/2/35		7/20/35	8/26/35	9/25/35	10/22/35	10/29/35
Hemoglobin, %	44.0	45.0	Splenectomy	54.0	67.0	62.0	67.0	70.0
Erythrocytes (mill./c.mm.)	2.7	2.83		3.13	4.26	3.36	3.99	3.68
Color index	0.82	0.8		0.86	0 8	0.93	0.84	0.95
Icterus index	5.0	6.0		5.0				
Sedimentation rate	86.0	27.0		55.0	32.0	30.0	...	45.0
Leukocytes (thous /c mm.)	2.9	3.1		12.1	9.6	9.4	11.9	8.2
Platelets (thous /c mm.)	240.0	..		...	...	...	359.0	
Differential count (%).								
Neutrophils, non-segmented	7.0	4.0		7.0	8.0	1.0	3.0	1.5
Neutrophils, segmented	62.0	55.5		72.0	57.0	69.0	74.0	59.0
Eosinophils (abs. Nos. in brackets)	1 (50)	3 (70)		3.5 (400)	3.5 (560)	2.5 (190)	1.5 (160)	3.5 (250)
Monocytes	8.0	9.0		12.5	10.0	8.0	5.5	6.5
Lymphocytes	22.0	28.5		5.0	21.5	20.5	16.0	29.5

Banti's disease was diagnosed and on July 5, 1935, a splenectomy was performed. Following the operation an empyema developed in the left pleural cavity. The empyema was drained, there were no tubercle bacilli in the pus. The patient recovered; the enlargement of the liver diminished.

When she was discharged, there was no jaundice, the blood picture was almost normal (Table 2). Two sternal punctures were performed; the results will be discussed later.

She is still without complaints 14 months after discharge from the hospital; no ascites has reformed. The only complaint is a moderate lassitude.

Examination of the Removed Spleen. Size: 30 by 25 by 10 cm. Several small accessory spleens were found. The surface is smooth, the cut surface of a brownish-red color without the usual pattern. The tissue is fragile, firm. No distinct trabeculæ. *Microscopically* the capsule is normal. The pulp shows a marked increase of the reticulum cells. No congestion, no increase of phagocytosis. The Malpighian bodies are few and small, without the usual pale centers. Several small scattered nodules seen. These partly confluent nodules consist of epithelioid cells with several giant cells of Langhans' type surrounded by lymphocytes. No necroses. Most of these typical tubercles are in intimate relation to the lymphoid follicles. There is no increase of the connective tissue. No tubercle bacilli found. An accessory spleen gave the same findings, but more pronounced.

Diagnosis. Miliary tuberculosis of the spleen.

Case 3.—A man, aged 46, entered the hospital on August 28, 1934 (Holbæk Amtssygehus, Jour. 1262/1934). Five years earlier the patient had suffered from an attack of feverish pleurisy. Since then loss of weight (10 kg.) and lassitude. On admission his chief complaint was right abdominal pain. He had similar attacks of pains before and was believed to suffer from a renal calculi. He also complained of slight fever, cough and nocturnal sweat.

Physical Examination. A large tumor in the left side of the abdominal cavity was palpated. The skin was pale but not icteric. Laboratory findings include: Hemoglobin, 81%; red blood cells, 3.41 mill. per c.mm. blood. Sedimentation rate, 39 mm. in 1 hour. The fragility of the red blood cells was normal (lower limit, 0.30%; upper limit, 0.45% of saline) blood urea, 20 mg.%. Wassermann reaction negative. Pirquet reaction negative (tested twice).

At operation, the palpated tumor was found to be an enlarged spleen, which was removed. The spleen weighed 1700 gm. (26 by 18 by 7 cm.). The patient recovered. On discharge, the sedimentation rate of the red blood cells had decreased to 3 mm. in 1 hour.

Microscopic Examination. The tissue is transformed to partly discrete, partly confluent nodules of epithelioid cells, with a varying number of mostly typical Langhans' giant cells. These nodules are so numerous that the ordinary tissue of the spleen is reduced to a minimum. In some areas nothing but a fibrillary connective tissue is left between the nodules and is uniting them. In other areas atrophied pulp tissue found with dilated sinuses and atrophic follicles. No signs of necroses in the nodules, but scattered incipient dry necrosis of the connective tissue between the tubercles observed. There is a slight infiltration of lymphocytes between the nodules and a few plasma cells (F. Gregersen).

Case 4.—A woman, aged 57, since 1931 has complained of increasing lassitude. She has been unable to work because of giddiness, ringing in the ears and dyspnea on exertion. The appetite has decreased. Admitted to hospital on April 4, 1936 (Kommunehosp. Dept. II Jour. 113/1936).

Physical Examination on Admission. Marked pallor of the skin and pronounced jaundice. Height, 158 cm., weight, 50 kg. There is slight fever (38° C.). The rest of the examination reveals nothing of interest.

Laboratory findings include: Wassermann reaction negative. Blood pressure, 165/85. Urine negative. Test meal (45 min.) 50 c.cm. free acid 8 to 10 and total acid 20 to 35. Roentgen ray examination of the bones was negative. The fragility of the red cells was much increased: Lower limit 0.44 to 0.56, and upper limit 0.76 to 0.80% of saline (3 different examinations). The blood showed a hyperchromic anemia with good bone-marrow response (Table 3).

Sternal marrow puncture showed an extraordinary hyperplastic bone marrow with an abundance of cells. Erythropoiesis was very much increased, partly megaloblastic in type. Differential count: Hemocytoblasts and megaloblasts, 8.4%; erythroblasts, 58.4%; erythroblasts in mitotic division, 1.4%; myeloblasts, 1.4%; promyelocytes, 3%; myelocytes, 6.6%; eosinophil myelocytes, 0.8%; neutrophil metamyelocytes, 12.8%; neutrophils, 4.2%; eosinophils, 0.2%; lymphocytes, 2.8%.

TABLE 3.—BLOOD FINDINGS IN CASE 4.

Date	7/30	Treatment with liver extract and stomach extract	9/7	10/7	11/7	12/7	2/4	3/13	Splenectomy	4/13
Hemoglobin, %	45.0		60.0	70.0	70.0	80.0	55.0	55.0		55.0
Erythrocytes, mill./c.mm.	2.0		2.4	2.6	2.6	2.8	2.4	2.4		2.4
Color index	1.15		1.25	1.35	1.35	1.45	1.12	1.12		1.12
Volume of packed cells	17.17		23.0	24.0	24.0	26.0	.	23.0		
Volume index	1.17		1.25	1.35	1.35	1.45	1.15	1.17		1.17
Reticulocyte, %*	26.1		...	46.0	42.0	..	..	31.0		
Sedimentation rate	80.0		127.0	121.0						
Icterus index	12.0		...	20.0	16.0					
Platelets (thous./c.mm.)	..		188.0							
Leukocytes (thous./c.mm.)	10.7		...	9.0	8.5	..	..	6.1		8.1
Differential count (%):										
Neutrophils, non-segmented	12.0		...	21.0	31.5					
Neutrophils, segmented	60.5		...	43.0	37.5	..	..	78.0		
Eosinophils	4.5		...	3.0	3.0					
Basophils	..		...	1.0	..	..	..	1.0		
Monocytes	4.5		...	12.0	11.0	..	..	2.0		
Lymphocytes	15.7		...	13.0	14.0	..	..	15.0		
Erythroblasts	..		...	2.0						

* Daily determinations of the percentage of reticulocytes before the treatment showed from 26 to 37%. During the treatment the percentage rose to 46%.

The patient was treated energetically with iron tartrate and injections of liver extracts which caused a slight rise in the percentage of reticulocytes, but was followed by no noticeable improvement of the condition. Splenectomy was therefore performed, but immediately after the patient died from a thrombosis of the vena cava.

Autopsy (By the author, next day. Path. Inst. Kommunehosp., 326/1936) *Skin* was pale and markedly icteric. Pleural cavities and *lungs* revealed nothing of note. The *heart* was negative. In the peritoneal cavity was 200 cc. hemorrhagic fluid. The *gastro-intestinal tract* was negative. The *liver* was of usual size and form. On section, the color was yellowish-brown, the pattern obscured. There was a total thrombosis of the splenic and portal veins. The *kidneys* were negative. The femoral *bone marrow* was dark red and hyperplastic, mushy. The removed *spleen* weighed 400 gm. (15 by 13 by 6 cm.) and was of dark, purplish-red color. The surface was smooth, the cut surface deep red, the Malpighian bodies were obscured and no trabeculæ could be seen.

Microscopic Examination. Spleen: The pattern was totally obscured; the Malpighian bodies were very small and few. The pulp contained many red cells, and especially a great number of reticulum cells. Only very little phagocytosis. In connection with the few trabeculæ and the remnants of the lymphatic tissue numerous typical tubercles were seen, partly as discrete nodules, partly as confluent areas with giant cells of Langhans' type. No necrosis was noticed. No tubercle bacilli were found. *Liver:* The cells were arranged in the usual pattern. Slight increase of bile pigment. In the portal tracts there was a moderate infiltration of lymphocytes and, where this was pronounced, small nodules of epithelioid cells and giant cells. *Bone marrow* (lumbar vertebra): Very cellular, marked hyperplasia.

No fat cells. The majority of the cells were normoblasts and megaloblasts. Among the white cells the more mature cells predominated. *Bone marrow* (from femur): The same picture as in the marrow from the vertebra, yet the hyperplasia was more marked.

Diagnosis. Status post splenectomiam. Thrombosis of the portal and splenic veins. Miliary tuberculosis of the spleen and liver. Anemia and jaundice. Hyperplasia of the bone marrow.

Discussion. *Clinical Picture and Treatment.* In all 4 cases the chief complaints were marked *weakness* and *lassitude,* and considerable *loss of weight;* also anemia and in 3 of the 4 jaundice of varying degree. These symptoms have been present during long periods from a few months to several years. In addition, all showed periods with slight fever. Of other symptoms the following have been noticed: Hematemesis, ascites, purpura, achylia, *enlargement of liver and spleen,* coughing, dyspnea and nocturnal sweating. Finally, rather considerable changes in the blood picture were observed: *anemia* with hemoglobin percentages of about 40 to 50 (only Case 3 had 81%), *leukopenia* 2 to 4000 white blood cells per c.mm. of blood (only Case 4 gave normal counts), and moderate *thrombocytopenia,* in 2 of the cases (Cases 1 and 4) with purpura. These changes in the blood were so outstanding that the conditions were diagnosed as *pernicious anemia* (Case 1), *Banti's disease* (Case 2) and *acholuric jaundice* (Case 4).

A noticeable increase of the sedimentation rate of the red blood cells was found in all cases (126, 86, 39 and 127 mm. in 1 hour). This finding has not been mentioned in previous reports of tuberculous splenomegaly. Unfortunately, we are unable to analyze the causes of this change.

The diagnosis of tuberculous splenomegaly was not made until the operation or the postmortem examination, when the enlarged spleen with miliary tuberculosis was observed. This was also the case in all the previous reports of this disease.

Of the cases here reported, 3 were operated on. One died of a thrombosis in the portal vein, the other 2 lived and essentially improved. After 14 months 1 of these 2 patients was quite all right but for her complaining of a slight lassitude.

Winternitz,[41] in 1912, gave a report of 51 cases, from which we learn the following of the disease:

Tuberculous splenomegaly occurs in all ages from 1 to 80 years, but more frequently between 20 and 40. Males and females are equally affected. If no splenectomy is performed, the disease will be fatal in 6 months to 14 years. Now and then more acute cases are seen. Of 17 patients who were operated on, 10 recovered. The chief symptoms are weakness, loss of weight, pains or a sensation of heaviness in the left side of the abdomen. An enlarged spleen can be palpated in some cases. In most of the patients a moderate febrility and changes in the blood picture have been noticed.

Even if the symptoms caused by the enlarged spleen are improved by splenectomy, the prognosis will always be dubious, as most of the patients are suffering from tuberculosis in other organs. In Winternitz' material 40% of the patients had tuberculosis of the lungs, 10% to a considerable degree. Furthermore, Winternitz states that tuberculosis of the liver was found in 80%, of the lymph nodes in 57% and in different organs in 66%. In one patient only no tuberculosis was found outside the spleen.

The splenomegaly is considerable. Of 31 cases the weight of the spleen was 150 to 1000 gm. in 13, 1000 to 2000 gm. in 13, and 2000 to 4000 gm. in 5. The anatomic changes of the spleen as a rule are dominated by diffuse miliary tuberculosis of large areas of tuberculoid tissue with, or more frequently without, caseous necroses. Tubercle bacilli were found in 17 of 24 cases in which a Ziehl-Neelsen stain was made.

From past years reports of other 28 cases have been given.[2–4,6,9,11,13,15,16,19,22,24–27,29,31,34]

On all significant points these 28 reports confirm the statements of Winternitz, except that the age of the patients differs a little, most of the reports dealing with patients from 21 to 74 years. The clinical picture is the same. Generally the duration of illness before hospitalization was 6 months to 2 years; in a few cases up to 8 to 10 years. Of 16 patients who were operated on, 14 survived. Of these, however, 7 died of tuberculosis of the lungs or generalized tuberculosis sooner or later after the operation, 2 of them after 6 months. Two died after 1 and 2½ years, respectively (no statement as to the cause of death), 1 after 3 years without signs of tuberculosis, and 1 lived more than 7 years.

Though the prognosis is said to be very dubious without splenectomy, it will be seen that it is slightly better when splenectomy is performed. However, most writers regard tuberculous splenomegaly as an absolute indication for operation.

A few patients have been treated with Roentgen rays or radium. Hallermann[11] claims to have achieved a remission of 4 years' duration by means of Roentgen ray treatment in a case of tuberculous splenomegaly where the spleen weighed 2850 gm.; Head[12] treated a case of alleged tuberculous splenomegaly with radium and benzene, and Schwensen[35] one with Roentgen rays with consequent improvement, but Lubarsch[22] reported on a patient who was treated with Roentgen rays without effect.

It is of peculiar interest that Pirquet's reaction was found to be negative in 3 cases. The reaction was not tested in the rest of the material, which most probably is explained by the fact that tuberculosis was not taken into consideration or diagnosed until the operation or the autopsy.

The weight of the spleen in these 28 cases was from 640 to 2850 gm. Tubercle bacilli were found in 8 of 9 cases.

The blood changes will be discussed later.

In only one case was the proper diagnosis made before the operation (Krümmel[19]). This patient was suffering from a generalized tuberculosis, and the enlargement of the spleen was therefore believed to be of tuberculous origin too. In general, it will most probably be impossible to make the diagnosis tuberculous splenomegaly unless the patient is operated on or a spleen puncture made.

Banti's disease, splenomegalies of different etiology and various blood diseases are those most often confused with tuberculous splenomegaly. Some authors stress the age of the patient and attacks of slight fever as distinguishing tuberculous splenomegaly from the conditions mentioned, but these are doubtful criteria. Without puncture of the spleen or splenectomy it is hardly possible to make the differential diagnosis between the various forms of chronic splenomegaly, Banti's disease or whatever term may be preferred for this clinical picture.

Pathologic Anatomy. The outstanding feature is the splenomegaly, a rare form of tuberculosis of the spleen. Of 172 cases of tuberculosis in 404 autopsies, Klotz[17] found 69 with tuberculosis of the spleen, but none exhibited splenomegaly. Lubarsch[22] found only 2 splenomegalies in 300 cases of tuberculosis of the spleen, of which he distinguished 4 types of tuberculous splenomegaly: indurated, miliary, hemorrhagic and nodular. All 4 of our cases belong to the miliary form. Its characteristics are: Considerable enlargement (average weight about 1000 gm.), smooth surface, normal capsule. The cut surface is reddish-blue or purple; the pulp firm, friable, with pattern obscured. In some cases there is no evidence of the miliary tubercles by macroscopic examination; in others, a pattern very much like the normal is seen, but on more careful examination the small nodules prove to be typical small tubercles and no Malpighian bodies.

In none of our 4 cases was the diagnosis made on gross examination alone. On microscopic examination the very cellular pulp showed numerous, partly confluent typical tubercles with little or no necrosis, the Malpighian bodies were few and small.

The splenomegaly, which as a rule is considerable, is due to proliferation of the reticulum cells in the pulp and to the presence of tuberculous foci, which also consist of cells derived from the reticulo-endothelial system. The nodules in these 4 cases have been localized according to Gråberg[10] along the arteries, most of them in intimate connection with the Malpighian bodies. Furthermore, there were numerous red cells, but no increased phagocytosis or blood pigment. The connective tissue was not increased.

As already stated, many cases have tuberculosis in other organs, the liver being often attacked. This fact has caused some writers to describe a condition which they call "hepato-lienal tuberculosis." Furthermore, tuberculosis of the lungs and often of the lymph nodes is seen. In 2 of our 4 cases which came to auptopsy, tuberculosis of the liver and lymph nodes was observed but no tuberculosis of the lungs.

Blood Changes in Tuberculous Splenomegaly. As a rule, in tuberculosis of the spleen, no other blood changes are seen than those found in tuberculosis in other organs. Heymann and Bussel[14] examined the blood of 19 children suffering from miliary tuberculosis of the spleen and found no other changes than those observed in children attacked by exosplenic tuberculosis.

On the other hand, the clinical picture in tuberculous splenomegaly will usually be dominated by significant blood changes. While the literature gives the impression that most any blood picture can be met with, more careful study shows that the typical blood picture is, as in Banti's disease, one of inhibited marrow function.

Weil,[33] in a study of 2 cases of leukemia with tuberculous splenomegaly, drew the unsupported and improbable conclusion that the tuberculosis caused the leukemia. As tuberculsosis of the spleen is not uncommon, it would be peculiar if all leukemic splenomegalics should be free from tuberculosis. Such enlarged spleens will easily be mistaken for tuberculous splenomegalies with secondary blood changes.

Polycythemia has occasionally been noted. Among Winternitz' 51 patients, 6 had from 6 to 8.2 million red cells per c.mm. Rosengart[27] observed a case with 10 million red blood cells and 200% hemoglobin. Szczcklik[34] reported 7.15 million red blood cells and doubtful cases of tuberculous splenomegaly with polycythemia have been reported by Head[12] and Léon-Kindberg.[21] While some authors, especially the French, regard polycythemia as the typical blood picture in tuberculous splenomegaly, this is denied by others; *e. g.*, Heymann, Lubarsch and Sternberg cannot accept that tuberculosis of the spleen is the cause of the polycythemia. These authors rather believe in a "primary" polycythemia, in which condition the spleen is probably a "locus minoris resistentiæ" and hence is affected by tuberculosis more often than are normal spleens. Be this as it may, reports of polycythemia in splenic tuberculosis in late years have become very few, while the number of cases is still increasing in which other blood changes are observed.

Among Winternitz' 51 cases, blood examinations were made in 27, 11 of which showed anemia, leukopenia or thrombocytopenia. In the reports of other authors (totaling 23 cases), blood examinations are given for 19 patients of which one had polycythemia (Szczcklik[34]), 2 leukopenia (Weil[36]), 2 gave normal findings (Bjering,[2] Carling[4]) and the rest (16 cases), exhibited similar changes to the majority of Winternitz' material, namely, anemia and leukopenia. Furthermore, the 4 cases in this report all belong to this group.

In all, we know of blood changes in 23 cases of tuberculous splenomegaly in addition to Winternitz' 26 (Table 4). Of these 23 patients, 20 gave blood pictures similar to those which are seen in Banti's disease. Among the 20 cases, there are 17 anemias (hemoglobin 40 to 70%), some of them hyperchromic (*e. g.*, Author's Cases 1 and 4); 9 patients had leukopenia (fewer than 4000 white blood cells per c.mm.). Hemorrhages occurred in 4 patients who exhibited a decreased number of platelets (Kellert,[16] Naegeli,[24] Author's Cases 1 and 2); and finally jaundice was observed in 6 patients (Carling,[4] Goebell,[9] Author's Cases 1, 2 and 4).

There are also reports of cases of tuberculous splenomegaly with a clinical picture similar to that of Banti's syndrome, but with no exact statement of the blood findings (Cynman,[5] Krümmel,[19] Carling[3]). These and 4 other cases whose reports were not available are not included in the table. As far as one can see, these cases have shown the same clinical picture as did our cases: 2 cases similar to Banti's disease (Bunch and Rennold); a pernicious anemia case (Fabre, Malaussene and Garnodier); and a case with purpura (Villa).

In 3 of the 4 cases dealt with in this report many blood examinations have been made; and in two, bone-marrow examinations. This procedure has rendered it possible to investigate more carefully the development of the blood changes in this disease.

All 3 patients (Cases 1, 2 and 4) were very pale on admission, with about 50% hemoglobin. The color index was 1.2, 0.82 and 1.15, respectively. The fragility of the red cells in one case was considerably increased, and normal in the other two. Case 4, which showed the increased fragility, was distinct from the others also in having an unusually high percentage of reticulocytes (26%) at a time when no treatment had been given. The number of white blood cells, too, differed from the findings in the rest of the group, being increased or at any rate at the upper limit of normal. The skin was icteric, in the blood were numerous typical spherocytes, and the bone marrow was hyperplastic and full of erythroblasts, this being the case in the sternal punctate as well as in the marrow examined during the autopsy. This case, therefore, had the characteristics of acholuric jaundice (spherocytic anemia). The past history of this patient as given in the hospital record gave no evidence of similar diseases in her family which is not of great importance, as no relatives have been examined. There were no signs of gall stones or ulcers of the legs, common symptoms in acholuric jaundice, whereas their absence can hardly preclude this diagnosis. On the other hand, the tuberculosis of the spleen (and liver) does not belong to the typical picture. The case may probably be interpreted as a case of acholuric jaundice with complicating tuberculous splenomegaly. We have no possibility of proving a connection between these two conditions. Certain interest is connected with

TABLE 4.—CASES OF TUBERCULOUS SPLENOMEGALY EXCLUSIVE OF WINTERNITZ' CASES.

Case No.	Author.	Age.	Weight of spleen, gm.	Tubercles in the spleen.	Tub. bacilli in spleen.	Hb., %.	Red blood cells, mill.	White blood cells.	Platelets.	Skin.	
1	Bjering, T.[2]	29	2,650	Miliary	?	80	4.43	4,100	÷ Hemorrhages		Pirquet reaction ÷
2	Carling, E. R., and Hicks, J. A. B.[4]	65	c. 2,000	Present	?	66	4.10	8,200		(+) Jaundice	
3	Idem	28	c. 2,000	Miliary	?	90	5.82	4,600			
4	Drebschok, F.[8]	42	Large	Present	?	56	2.82	5,800			
5	Weil, P. E. *et al.*[40]	74	1,160	Scattered small	+	70	3.23	13,000			
6	Idem	56	1,350	Scattered small	+	90	6.50	48,000		(÷) Jaundice	58% lymphocytes 4% myeloblasts 42% myelocytes
7	Hallermann, A.[11]	50	2,850	Several	?	60	4.20	4,300			
8	Hoencke, E.[15]	32	370	Several	?	?	3.60	?			
9	Kellert, E.[16]	26	1,050	Several	+	50	4.60	6,500	+ Hemorrhages		
10	Lubarsch, O.[22]	23	Large	Miliary	?	70	4.90	4,300			
11	Idem (Goebell[9])	30	1,050	Present	?	?	5.70	2,800		(+) Jaundice	
12	Naegeli, O.[24]	?	Very large	Several	+	70	4.50	?	+ Hemorrhages		
13	Permin, C.[25]	21	1,250	Large necrotic	+	60	?	5,000			
14	Price, A. E., and Jardine, R. L.[26]	41	30 cm.	Miliary	?	42	2.25	1,950		(÷) Jaundice	54% myelocytes
15	Idem	41	6 times normal size	Miliary and necrotic	?	60	3.36	2,950		+ Jaundice	
16	Idem	43	2,200	Confluent	?	70	4.42	3,600			
17	Sartorari, F.[29]	46	Large	Confluent	?	Anemia		4,000			
18	Schubert and Geipel[31]	51	640	Miliary	+	?	3.50	2,500			
19	Szczeklik, E.[34]	39	1,955	Present	?	?	7.50	?			
20	Engelbreth-Holm, J.	68	460	Miliary	+	57	2.30	2,000	115,000	(+) Jaundice	
21	Idem	44	30 by 25 by 10 cm.	Miliary	+	44	2.70	2,900	Purpura	(+) Jaundice	Fragility of red cells normal Pirquet (+) ÷
22	Idem	46	1,700	Several small	?	81	3.41	3,800	240,000	Pale	Fragility of red cells normal Pirquet ÷
23	Idem	57	490	Miliary	+	45	2.00	10,000	188,000	+ Jaundice	Fragility: hemolysis at 0.76% to 0.9% total 0.56% to 0.44% Saline. Reticulocytes: 260%

the fact that Thompson[35] in a survey of 45 cases of "acholuric jaundice," separates 15 as atypical cases of anemia with jaundice, clinically very similar to the hereditary disease. Of these, 3 died of reticulum-cell sarcoma in the spleen, and in one case a *disseminated tuberculosis of the spleen* was found at autopsy. However, the spleen was not much enlarged. These patients showed no typical spherocytosis and thus most probably are different from the Aüthor's case mentioned above. Anyhow, these findings show that it is not justifiable to deny *a priori* a connection between the blood changes and the tuberculosis of the spleen in our Case 4. Further support of this view is perhaps given by the case reported by Schiappoli,[30] who observed a hemolytic anemia in a patient suffering from Hodgkin's disease localized to the spleen and liver. Hemolytic anemia of considerable degree connected with, perhaps caused by, a hyperplasia of reticular tissue in the spleen, is nothing unique, at any rate according to the above-mentioned observation.

The remaining 3 of the cases reported here are much alike. The percentage of the hemoglobin on admission was 57, 44 and 81, respectively. The red cell counts were 2.3, 2.17 and 3.41 million; and the color index, 1.2, 0.82 and 1.2, respectively. The number of white cells per c.mm. was 2300, 2900 and 3800. The platelets were counted in two of the patients: 233,000 decreasing to 155,000 (Case 1), and 240,600 (Case 2). In the second case a hemorrhagic purpura was noticed. The reticulocytes were counted in one case only (Case 1), which showed normal findings, 0.2 to 0.4%. The fragility of the red cells in Cases 2 and 3 were normal. The icterus index of Cases 1 and 2 was between 11 and 5. Case 1 was treated with pylorin and liver without effect. The results of a sternal puncture in Case 2 are given in Table 5.

All of these cases thus show one or more signs of an inhibition of the bone-marrow function. No "specific blood disease" can be diagnosed. The changes are very similar to those of Banti's disease, anemia splenica or whatever term is preferred for these conditions.

The rôle of the spleen in the development of the changes of the peripheral blood is conspicuously seen in Case 2 in which the patient in spite of her almost desolate condition survived a splenectomy. Following this, remarkable changes in the blood picture were noticed: The hemoglobin rose from 44 to 70%, the red blood cells from 2.7 to (4.26) 3.69 million, the color index from 0.82 to 0.95 and the white cells from 2900 to 10,000. The number of platelets increased from 240,000 to 360,000. The number of eosinophils counted direct (Dunger[7]); rose from 50 to 70 to 400 to 500. However, complete recovery was not achieved, the sedimentation rate was unaltered, presumably because the tuberculosis of the spleen was not the only manifestation of the disease. At any rate a considerable improvement, subjectively as well physically, was obvious.

It is of peculiar interest that two sternal marrow punctures were performed on Case 2. Thus, we have knowledge of the composition of the bone marrow before the splenectomy and 3 months afterwards. The results of these examinations are recorded in Table 5.

TABLE 5.—STERNAL BONE MARROW CYTOLOGY OF CASE 2.

Date	4/29/35		7/5/35	10/29/35	
Cells in punctate	Normal			Normal	
Hemocytoblasts	3.5%			0.0%	
Erythroblasts	31.0%	36.5%		13.7%	13.7%
Myeloblasts	2.0%			2.0%	
Promyelocytes	8.0%			0.7%	
Myelocytes	13.0%			6.0%	
Neutrophils, non-segmented	14.0%			5.0%	
Neutrophils, segmented	17.0%	54.0%		31.3%	45.0%
Eosinophils	1.0%			0.7%	
Basophils	0.5%			0.3%	
Monocytes	0.5%			7.7%	
Lymphocytes	9.5%			31.3%	
Plasma cells	0			0	
Mitoses	5 per 500 cells			1 per 500 cells	
			Splenectomy		

While the number of cells is nearly the same in the two punctates, there is a marked decrease in the immature cells after splenectomy; also in the number of mitoses.

These findings are interesting. As seen from Tables 2 and 5, anemia and leukopenia were found in the peripheral blood at a time when the bone marrow showed a relatively immature picture with "shift to the left;" 6 months later, when splenectomy had been performed, the anemia and the leukopenia were diminishing, while the marrow picture was much more steady without signs of increased function.

Similar changes have been observed once before by the author, in a case of splenomegalic anemia and leukopenia of unknown etiology. This patient, a woman of 57, entered the Finsen Institute, Copenhagen (Surg. Dept. No. 9938), in 1934. The blood picture showed: Hemoglobin, 44 to 60%; red blood cells, 1.2 to 4.0 millions; color index, 0.75 to 0.8; white blood cells, 800 to 1100; and platelets, 186,000 to 300,000. The percentage of reticulocytes was 1.0 to 2.5. The fragility of red blood cells was normal. By differential counts a severe neutropenia and now and then a few myelocytes were found. The sedimentation rate of the red blood cells was much increased: 98 to 158 mm. in 1 hour. Physical examination revealed a large splenomegaly. The nature remained obscure, as the patient was not operated on. She is still alive (January, 1937). A sternal puncture performed in November, 1934, showed the same hyperplasia of the bone marrow as in the aforementioned cases. The punctate was extremely cellular, with 4.5% hemocytoblasts, 21% erythroblasts, 7.5% myeloblasts and 33% promyelocytes. This finding is apparently but little in accord with the condition of the peripheral blood, which contained very rarely more than 150 to 200 granulated leukocytes per c.mm., against the normal 2500. There were rather numerous mitoses in the punctate.

Discussion. The relation of the spleen to the function of the bone marrow is an obscure question. As to the erythrocytes, the opinions diverge. Krumbhaar[18] and others found a transitory anemia following splenectomy and conclude that the normal spleen does not have an inhibitory action on erythropoiesis in the bone marrow. Others found rising numbers of erythrocytes following splenectomy (see Krumbhaar,[18] Lauda[20]), and Lauda in his "Physiologie der Milz" concludes that the normal spleen has an inhibitory effect on the function of the bone marrow.

Following removal of the spleen (whether normal or diseased) most authors have observed a rise in the number of leukocytes and of the platelets. Furthermore, immature forms of both erythrocytes and leukocytes are often seen; this is regarded as the result of release from an inhibitory effect of the spleen. Also Frank[8] pointed out that an increase of the reticulo-endothelial elements in the spleen as a rule is followed by leukopenia and thrombopenia.

The cases mentioned in this report seem to support this view, but the bone marrow, as seen by the sternal punctures is hyperplastic, *i. e.*, formation of immature red cell forms; at any rate is not inhibited.

According to the above case where the bone marrow was examined before and after the splenectomy what actually happens is that the marrow, which before the operation has been full of normal but immature marrow cells, following the removal of the spleen pours great number of cells into the circulating blood. This explains the increasing number of partly immature cells in the blood as well as the decreasing number of cells in marrow. Accordingly it seems justifiable to assume a controlling function at least by some spleens *on the emission of cells* from the bone marrow. If this emission is regarded as a simple result of the maturation of the marrow cells, the function of the spleen may be looked upon as a controller of the maturation of the cells in the marrow. This point of view is to a certain extent endorsed by the fact that marrow punctures in cases of spenomegaly with leukopenia reveal an increase of the immaturity of the cells in the marrow, as compared with the findings in normal sternal punctates.

It must be stressed that we have no support for assuming the function of the spleen, and especially the pathologic function, to be an inhibition or control of the *production* of cells in the marrow, but only a controlling of the emission of cells, this being an independent function, or a function secondary to the maturation.

For the present discussion it is of interest that this function of the spleen apparently increases when the spleen is enlarged as a result of miliary tuberculosis. It has been mentioned that similar changes will take place when the enlargement is due to reticulum cell sarcomas. Furthermore, it is known that the "fibrosplenia" in Banti's disease and certain other splenomegalies, as in malaria, Gaucher's disease, etc. can produce similar blood changes. These facts will probably be of value when considering the question as to which cells in the spleen are actually carriers of the marrow-controlling function found in the normal spleen and accentuated in different cases of splenomegaly.

Most probably the function discussed originates in the reticulo-endothelial elements, and above all in the reticulum cells, these being the only elements in the spleen pulp which are proliferated in the rather different diseases in which the almost identical influence on the marrow is seen. Both in Banti's disease and in the splenomegalies of tuberculosis and malaria a considerable proliferation of the reticulum cells occurs. Of course, the same is the case in reticulum-cell sarcomas. In Gaucher's disease, too, these cells are attacked and proliferated. It is in accordance with the view here set forth that neither by hyperplasia of the lymphatic tissue, nor by other hyperplasias of the spleen, where the reticulo-endothelial elements are not involved, or only slightly, will blood changes appear such as those mentioned above.

In this connection it is interesting that Wahlberg[37] has found remarkable changes in the Golgi apparatus and in the arrangement of chondriosomes inside the reticulum cells in spleens from cases of essential thrombopenia. These changes most probably are signs of an abnormal function; at present, however, it is hardly possible to decide whether these changes cause or are caused by the blood anomalies.

Conclusions. From the findings in these 4 cases of the rather rare condition of tuberculous splenomegaly, it seems justifiable to conclude that

Splenomegalies caused by miliary tuberculosis, like certain other splenomegalies where proliferation of the reticulum cells has taken place, may give rise to an apparent inhibition of the bone-marrow function, with subsequent peripheral blood changes.

*These blood changes may probably be interpreted as the result of an inhibition of the emission or of the maturation of the blood cells in the bone marrow, but not of the production of cells there.**

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* It should be noted, however, that these conclusions are based on the changes following removal of tuberculous and highly altered spleens from anemic patients. One can easily conceive of other mechanisms to explain the return of the blood picture toward normal after removal of disease-containing tissue. Similarly, the shift of the cellular composition of the bone marrow toward normal after these splenectomies could be adequately explained as due to the lessened demand during any period of recovery from anemia, without necessarily invoking a release from a specific inhibition of erythrocyte emission or maturation.—EDITOR.

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A PECULIAR FORM OF MEDIAL CALCIFICATION IN THE AORTA OF A DOG.

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SCLEROSIS of the aorta is one of the commonest afflictions of man. Changes begin in the early years of life and the lesions are readily discernible at necropsy in the aorta of practically every adult. In animals, however, this condition in any advanced degree is comparatively uncommon, and in dogs in particular it is rarely outstanding at any age. Lyding[7] reported endarteritic changes in 35 of 100 cattle examined, and in 2 horses and 2 dogs out of groups of 10 each; Strauch[9] found changes in but 2 of 100 dogs. In our experience, routine postmortem examinations of dogs seldom reveal even mild degrees of aortic changes. Hutyra and Marek[3] frequently noted calcification in the walls of the large blood-vessels in cattle and heavily worked draft horses.

Fox[2] performed 1806 necropsies at the Philadelphia Zoölogical Gardens and observed 31 instances of "degenerative angiitis, arteriosclerosis." In this group were included primates, carnivores, marsupials, and ungulates. He described the lesions as "roughened, rather opaque, intimal changes with degeneration of the media." There was usually lacking "that well-outlined, heaped-up, ulcerating, roughened intima so characteristic of the late human atheromata." He occasionally saw fatty, yellow streaks in the lining, but none of them appeared to be calcified. He noted that the aorta was more frequently affected than other vessels and that the lesions were usually found in the arch and thoracic portion. There was never any marked deformity of the aorta, and aneurysms were observed only 4 times.

Köllisch,[5] Strauch,[9] and Krause,[6] writing separately, noted that in dogs, beginning at about the fifth year, slightly raised, pillow-like (kissenartige) thickenings appeared on the intimal surface of the aorta. Hutyra and Marek stated that there are slight connective-tissue proliferation, deposition of small amounts of lipoids, and an increase of elastic fibers at points where the caliber of the arteries was reduced. They remarked further that these changes usually remained entirely microscopic, the intimal changes alone becoming *visible to the naked eye only on the rarest occasions.*

Joest,[4] Krause,[6] and others have described occasional instances of medial calcification in the aortas of dogs. Joest studied 2 cases of medial calcification in the aortas of young dogs and concluded that the lesions were dependent on parenchymatous inflammation of the media as the result of infection and did not represent changes due to old age. There are parasitic diseases which affect the aorta and smaller arteries of animals; but, as many authors have noted, the lesions which are produced bear no relation to true arteriosclerosis. Zinserling[10] firmly believed that there was no relationship between the lesions found in the aorta of animals and those of aortic sclerosis in man. On reviewing the literature for the past 25 years we have been able to find only 2 cases reported in which lesions in the aorta of a dog resembled arteriosclerosis in man.[1,8] Consequently, the case to be reported herein is of unusual interest:

Case Abstract. The dog in this case was approximately 10 years old and was in apparent good health at the time of his death. He had been in the laboratory for 8 years and had been the subject of several studies, none of which, however, could have influenced the state of his arteries. He was killed by inhalation of ether. At necropsy, the gall bladder was found to be small and thick walled, and contained more than 100 small

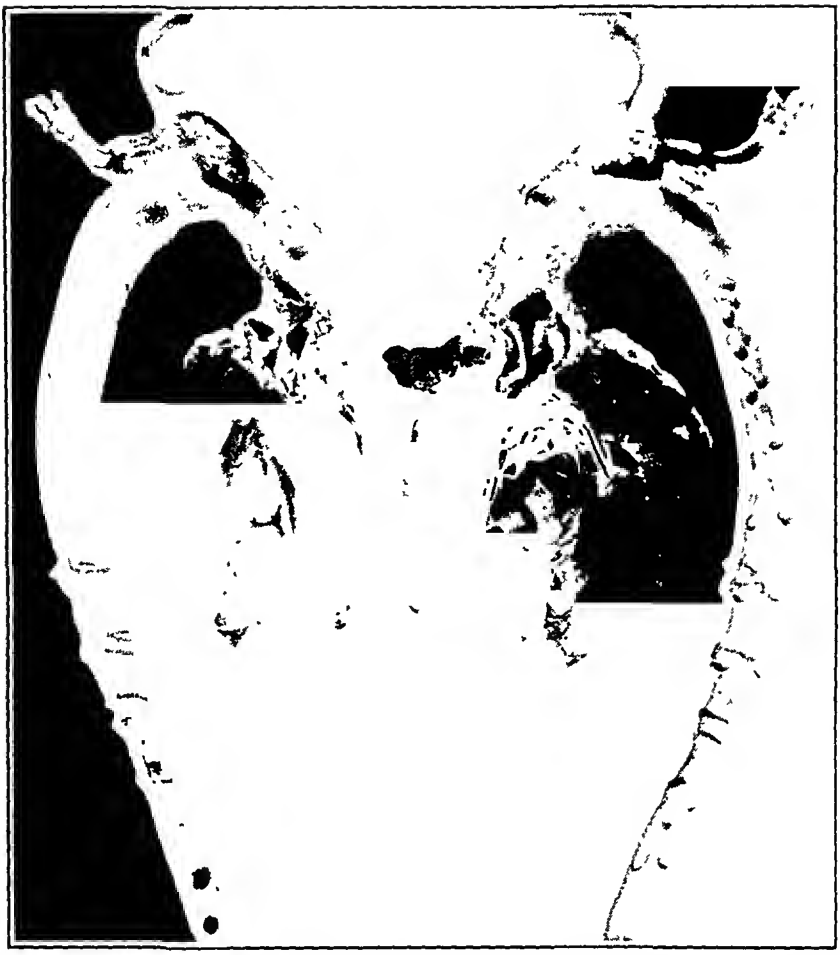


FIG. 1.—Heart and aorta cut sagittally, showing the thickened and calcified wall. (Lower abdominal aorta not shown.)

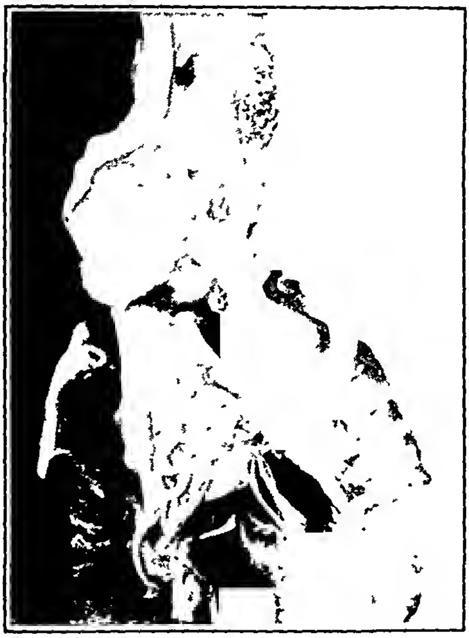
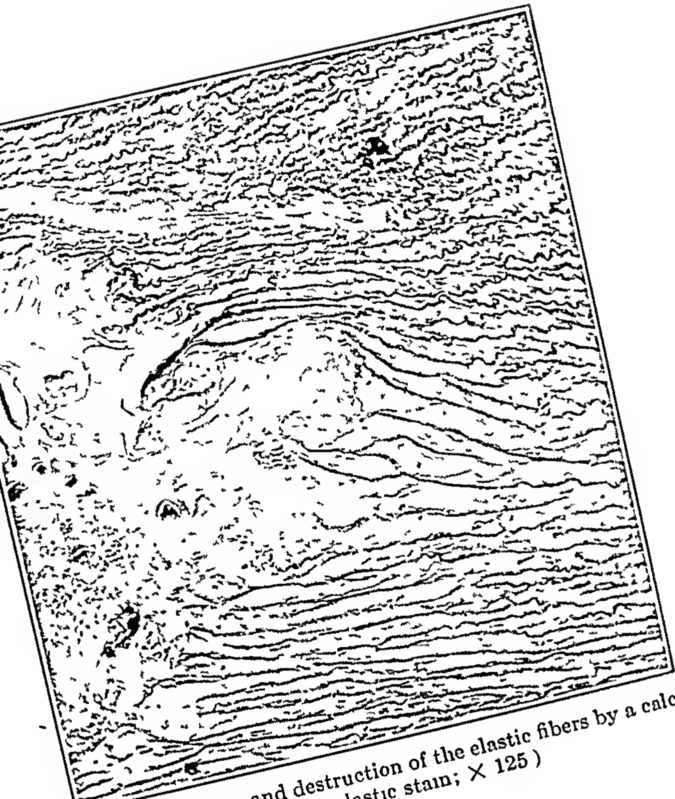


FIG. 2.—Heart and ascending aorta, showing calcification and aneurysmal dilatation of the wall.



G. 3.—Showing distortion and destruction of the elastic fibers by a calcified plaque. (Weigert elastic stain; × 125)

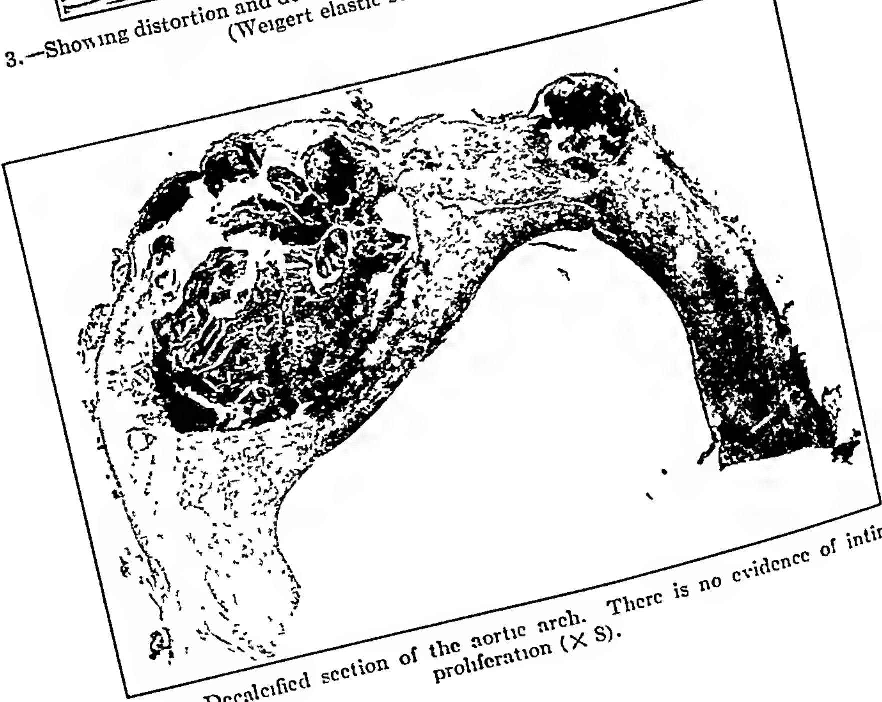


FIG. 4.—Decalcified section of the aortic arch. There is no evidence of intimal proliferation (× 8).

stones; the inner surface of the fundic region was ulcerated. Several small lymphomas were observed in the spleen, and the aorta revealed a severe degree of focal involvement (Fig. 1). No other pathologic changes were observed.

The wall of the ascending portion of the aorta was markedly thickened and roughened, and contained numerous, large, calcified plaques and nodules. Immediately above the aortic valve, the aorta was so distorted by the sclerotic process that a small aneurysmal dilatation was formed (Fig. 2). The intima, however, was not ruptured. There was a large group of calcified nodular masses surrounding the points of origin of the brachiocephalic arteries, and the process extended up in the walls of these vessels for a distance of 4 to 5 cm. The upper thoracic aorta disclosed slightly thickened walls and the intimal surface was comparatively smooth. The lower thoracic aorta down to the origin of the celiac axis was thinner, but at each segment where the intercostal arteries emerged the surrounding aortic wall bulged outward and was densely calcified. The abdominal aorta below the origin of the superior mesenteric artery was apparently normal.

It is peculiar that the lesions were absent in the lower part of the aorta and in the smaller arteries. However, as has been previously noted, Fox found the same distribution in his series. This is just the reverse of the ordinary distribution observed in the aorta of man, where the most severe sclerosis is often seen in the distal portion. In man, also, the calcified areas are not piled up as they were in this dog, and the so-called "atheromatous abscesses and ulcers" so commonly associated with aortic sclerosis in human beings were entirely lacking. The heart appeared to be slightly hypertrophied but was otherwise normal. The aortic valve leaflets were not affected even though the aortic wall behind them was definitely calcified. The coronary ostia were not compromised.

Microsopically, the changes in the aortic wall appeared to be limited almost entirely to the media. In every section taken from numerous areas along the course of the aorta the intimal lining could be followed quite easily and in only a few small areas was it slightly thickened. The upper thoracic portion of the aorta, which was free from calcified plaques, was slightly thicker than normal, mainly as a result of an increase in the collagenous fibers as revealed by the Van Giesen stain. A similar section stained for mucin did not disclose any appreciable increase in this substance in the interstitial spaces. The elastic fibers were brought into the foreground in another group of sections by the Weigert elastic tissue stain (Fig. 3). They appeared to be unusually tortuous and slightly fragmented but were otherwise not remarkable. The internal elastic lamina was readily discernible immediately beneath the intima and it was intact throughout its entire length. In sharp contrast to the areas just described were the portions of the aortic wall which had become calcified. These calcified nodules were found entirely within the media, and although they projected both inward and outward, they pushed the internal and external elastic lamina ahead of them. The main mass of calcification was composed of basophilic amorphous material which contained no cholesterol crystal clefts. It had that peculiar paraffin-like appearance so frequently seen in the aortic ring in cases of calcified aortic stenosis in man (Fig. 4). Smaller areas were more homogeneous and eosinophilic, but the absence of marrow spaces and osteoblasts disproved any bone formation.

In contrast to the relatively large amounts of lipoids ordinarily found in association with aortic sclerosis in man, sections of this dog's aorta which were stained with scharlach R revealed these substances in negligible quantities.

Sections of the kidneys, liver, brain, and other organs revealed no evidence of fibrosis or thickening of the smaller arteries. The wall of the gallbladder in the fundic region was deeply ulcerated, the muscle layers being invaded by neutrophils and fibrin. There was a dense layer of fibrous tissue beneath the bed of the ulcer which undoubtedly meant that the acute process was superimposed on a chronic one.

Comment. The lesions which have been described in the aorta of this dog were of unusual interest for three reasons: 1, the condition is extremely rare in dogs; 2, its morphologic features were for the most part dissimilar to those which are commonly found in aortic sclerosis in man; and 3, they closely resembled the lesions observed in the aorta in association with calcified aortic stenosis in man. The aorta was affected principally in its first segment, the non-calcified portions were practically normal, the calcified masses were brittle but not softened, and there were no atheromatous abscesses or ulcers. The lipoid elements were not increased, and the intima and internal elastic lamina were practically unaffected. Even though we were unable to determine the causative agent in this case, the morphologic evidence would appear to favor an infectious origin rather than sclerosis due to old age.

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A CASE OF XANTHOMA DIABETICORUM ASSOCIATED WITH DIABETES MELLITUS AND ACROMEGALY.

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Xanthoma diabeticorum, associated with diabetes mellitus and acromegaly, has been reported in three previous instances.[2,3] Xanthoma diabeticorum is not rare, as in 1933 McGavick and Shepardson[1] collected 97 cases. Acromegaly, as such, is so common that cases are no longer reported.

Case Report. S. L., aged 29 years, white, male taxicab driver, was first admitted February 1, 1933, complaining of weakness, polydipsia, and drowsiness. A tonsillectomy was performed at the age of 10. There was no venereal history. He had no cardiac or pulmonary symptoms. About 2 years before admission he noticed he was gaining weight rapidly. His neck, nose, and ears (Fig. 1) increased in size while he became mentally sluggish. Two weeks before admission he began to take pituitary and thyroid extract. He lost 35 pounds in weight, became weak, thirsty, and drowsy. There was no history of headache, dizziness, nor vomiting. The sexual desire and power increased.

On physical examination the temperature was found to be 98.6° F., pulse 118, and respirations 28. The calvarium, ears, and nose were enlarged. The superciliary ridges and antral regions were large. The lower jaw was prominent. The lips were deeply fissured (Fig. 2). The tongue was increased in size in all dimensions. The teeth were carious. The thyroid was not palpable. The chest was well developed and expanded equally on both sides. The heart, lungs and abdomen showed no abnormalities. There was no thickening, or tortuosity of the peripheral blood-vessels. The hands and feet were enlarged, the fingers short and wide (Fig. 3). The patellar and Achilles reflexes were present and normal. The skin was dry, and there were no eruptions present. The ocular fundi were normal. Roentgenograms showed an enlargement of the soft tissues of the hands and feet; skull moderately large, with fairly thick bones in the vault. The sella turcica (Fig. 4) was moderately enlarged, but there were no evidences of bone erosion.

The urine showed +4 sugar and acetone. The blood urea nitrogen was 14.3 mg., creatinine 1.5 mg., and glucose 400 mg. All figures in this report for blood chemical substances represent amounts found in 100 cc. of blood. The blood Wassermann test was negative. The blood count was normal.

The patient left the hospital of his own accord after 7 days.

The second admission was April 4, 1933, for impending diabetic coma. The urine showed +4 sugar, +4 acetone, and +2 diacetic acid. He was rapidly desugarized and detoxicated by the use of insulin. The patient was placed on a diet of carbohydrate, 140 gm.; protein, 70 gm.; fat, 130 gm., with insulin dosage of 30, 30 and 40 units. The examination of the fundi at this time revealed some granular changes in the maculæ. The roentgenogram of the skull showed no changes over the previous admission.

The patient left the hospital after a few days of treatment.

On October 16, 1933, he was admitted to the hospital complaining of diarrhea and weakness. He had not adhered to the diet. The urine showed; +4 sugar, and +4 acetone. The blood studies showed; 366 mg. of sugar, and 480 mg. of cholesterol. The previous dietetic regimen was instituted. He signed his release on the sixth day when the blood sugar was 333 mg.

On June 20, 1934, he was admitted complaining of generalized weakness, generalized ulcerating and non-ulcerating nodules of the skin, polydipsia and polyphagia. The fairly hard nodules were located on the posterior lower third of the arms, and upper one-third of the forearms, and anteriorly over the lower third of the thighs, knee caps, and upper third of the legs (Fig. 5). Their size varied greatly and in some instances they were confluent. A yellowish pigment was located at the summit of all the non-ulcerated areas. The nodules came on so gradually that he was not aware of them until they were well marked. The blood chemical tests showed; sugar 222 mg., and cholesterol 480 mg. After desugarization a biopsy was performed on one of the nodules, which showed the lesions to be of xanthomatous origin (Fig. 6). The blood studies on June 25, showed; sugar 285 mg., and cholesterol 480 mg.

As an outpatient on July 2, 1934, the blood sugar was 333 mg., and cholesterol 480 mg. On August 2, the blood cholesterol was 480 mg.

On November 25, 1934, he was admitted complaining of nodules which had been present since May, 1934. There was no itching of the skin. There was a complete loss of sexual desire and power. The gums were studded with nodular, discrete, and confluent lesions on a red base with a yellowish summit. The nodules bled easily. A roentgenogram showed no increase in size of the sella turcica since February 2, 1933. On December 1, the total blood lipoids were 875 mg. On December 7, 1934, the blood studies showed; glucose 666 mg., calcium 11.5 mg., cholesterol 667.7 mg., and total blood lipoids 934 mg. The urine showed 2.5% of sugar. The blood count was normal. The blood lipoids later rose to 1000 mg.

The eye examination on December 7, 1934, by Dr. R. M. Rogers, showed normal movements and reflexes in both eyes. The corneæ, anterior chambers, irides, and lenses were normal. There were no vitreous opacities. The right optic nerve was clear in outline with a normal physiologic cup. The nerve head was slate gray in color. The retina showed an unusual pink color overlaying a gray pigment. There were fine granular changes in the macular region. The veins were darker than the arteries, light lavender in color, neither full nor tortuous, nor increased in size. The outline of the arteries was normal, but their walls were gray and flat. The left optic nerve was the same as the right. The vessels in the left were more engorged than in the right, and the lavender color was deeper. The inferior temporal vein was more engorged than any other vessel in the fundus. The macula showed fine granular changes. The visual fields showed bitemporal contraction. The vision was normal in both eyes.

The patient was put on a diet of carbohydrate, 280 gm.; protein, 100 gm.; fat, 120 gm., with insulin dosage of 60, 40 and 50 units. The diet was changed on December 8, 1934, to carbohydrate, 150 gm.; protein, 60 gm.; fat, 60 gm., with insulin units 20, 20 and 20. In spite of large insulin dosage, the percentage of sugar in the urine varied from 1.4% to 10%. The blood sugar varied from 365 mg. to 666 mg. The urine volume varied from 2000 to 3000 cc. per 24 hours. The patient was discharged after 72 days with a diet of carbohydrate, 150 gm.; protein, 60 gm.; fat, 40 gm., with insulin dosage of 35 units three times a day. The blood sugar at the time of discharge was 400 mg. The patient always got extra food from some place, so sugar values did not indicate therapeutic responses. The situation could not be controlled.

The patient was admitted on December 4, 1935, and the laboratory data and therapy are given in Table 1. A repeated examination for prolan in the urine showed a small quantity present. Forty cc. of urine contained 1 mouse unit or 6 rat units. Follicle stimulation was produced, but no lutein cysts nor "blut punkte" were present.

The patient is alive on June 1, 1937, and the chemical status remains the same, although he is taking 150 to 160 units of insulin a day. The lesions of the skin have returned since the insulin is not given every second hour. The lips are deeply fissured. The disproportionate enlargement of the soft tissues of the ears, hands, nose, and feet which diminished considerably for a time, has regressed. Headaches are not present, and the mentality is not sluggish. He weighs 190 pounds. Sexual desire and power are absent.

Comment. The pituitary disturbance, which expressed itself as acromegaly, was the primary change in this case. The factor or factors which caused the pituitary change are unknown and may still be operative. The diabetes mellitus and the lipoidal changes are secondary. The over-secretion on the part of the pituitary apparently has subsided, perhaps because of cellular degeneration. as the enlargement of the hands and feet has decreased, and there is complete loss of sexual power and desire. The lipoidal changes

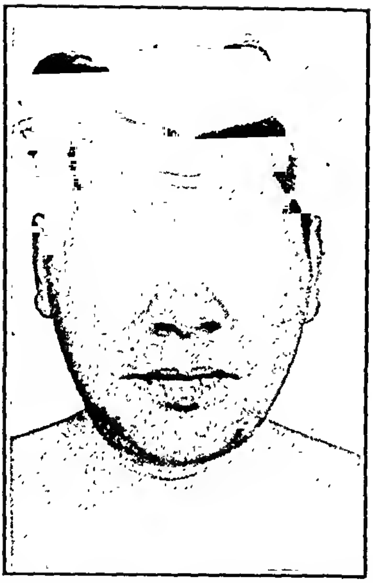

FIG. 1.—Shows size of nose, ears, neck and head.

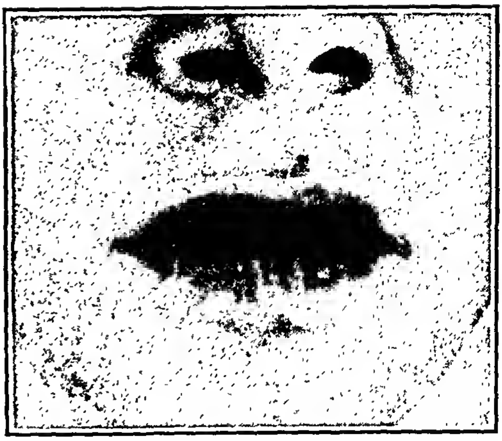

FIG. 2.—The deep fissures in the lower lip are clearly shown.

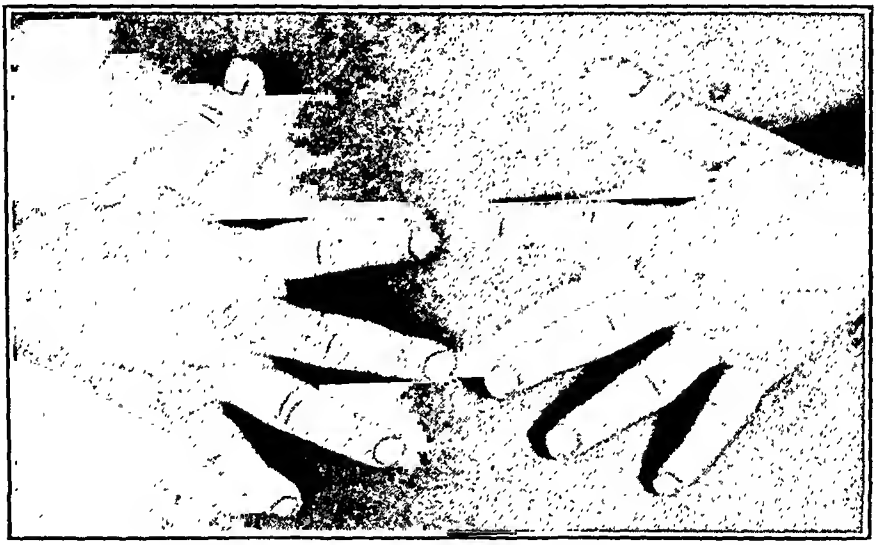

FIG. 3.—The hands are spadelike.

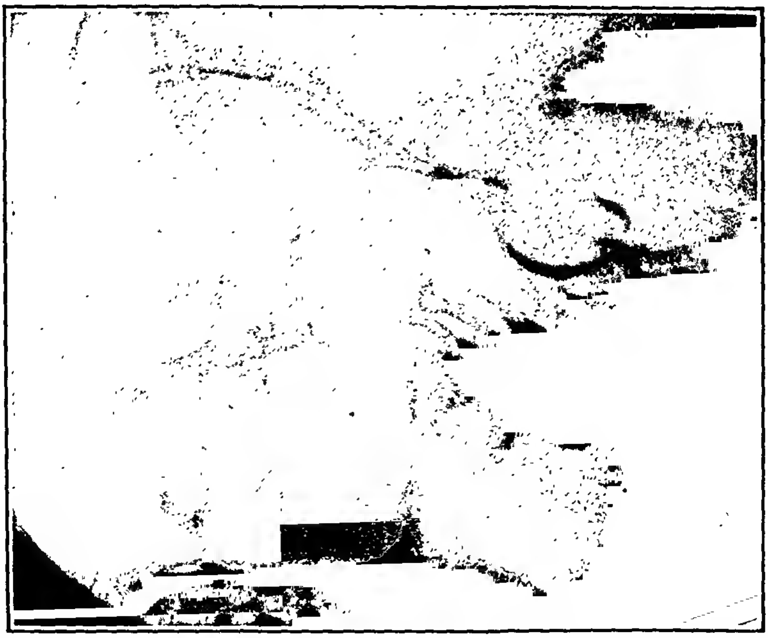

FIG. 4.—Illustrates the size and condition of sella turcica and clinoid processes.

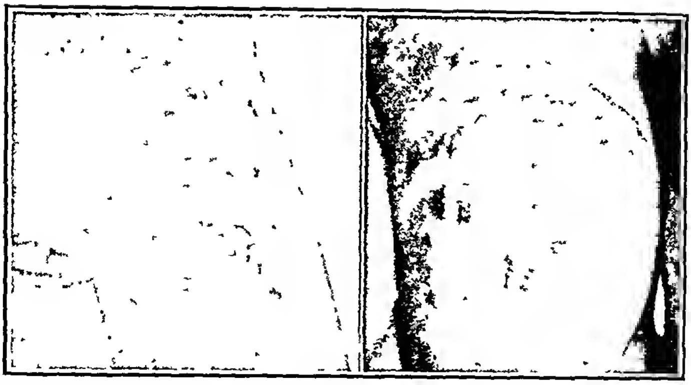

FIG. 5.—Illustrates multiple lesions over arms and forearms, thighs, knees, and upper legs.

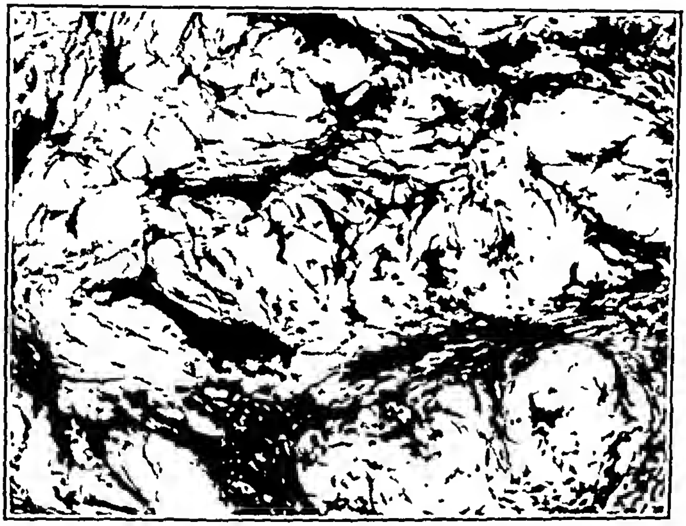

FIG. 6.—Section from cutaneous nodule showing foam cells present. Special fat stains showed lipoidal material in crystal-like arrangement.

FIG. 7. FIG. 8.

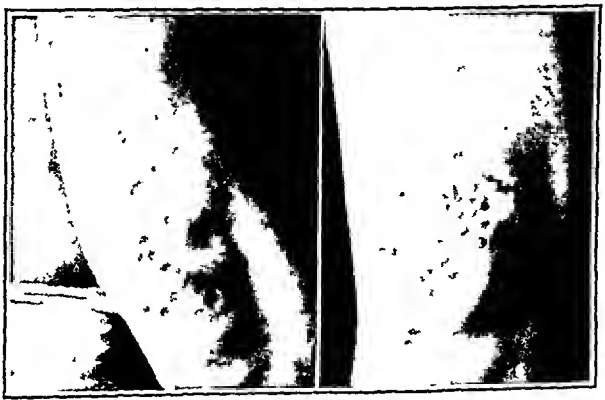

FIG. 7.—Shows a few lesions on posterior surface of arms and forearms.

FIG. 8.—Shows a moderate number of lesions on thighs and legs. Some were flat, purplish areas, others nodules with a yellowish summit.

in the skin and the excess lipoids in the blood could be restored to the normal condition by frequent moderately large doses of insulin. The lipemic state of the retina disappeared under the same therapy. There are no signs of arterial changes at the present time.

TABLE 1.—LABORATORY DATA FOR 180 DAYS.

Date.	Sugar in urine (%).	Blood sugar.	Total blood choles-terol.	Total blood lip-oids.	Insulin.	Basal met-abo-lism.	Wt. (lbs.).	Miscellaneous.
1935.								
12–5	1.4	440	990.0	..	50U t.i.d.	..	168¾	Cholesterol ester 660; full house diet, unweighed
12–7	..	400	666.7	934	"	..	..	Sedimentation test, 78.
12–14	2.5	500	...	..	"	33	187	No signs of hyperthyroidism.
12–20	1.9	410	...	..	"	..	194	
12–24	1.2	400	...	..	"	46	..	No signs of hyperthyroidism.
12–31	1.0	240	740.0	..	"	..	..	Acetone +4.
1936.								
1–7	1.3	500	...	..	60U t.i.d.	..	..	Acetone +3.
1–15	2.2	500	...	..	"	..	..	Acetone +2.
1–21	4.0	181	...	..	20U Q 2 H.	..	..	Sugar-free at times.
1–24	0.4	145	...	..	"	45	..	No signs of hyperthyroidism.
1–29	Neg.	222	...	..	40U Q 2 H.			
1–31	Neg.	133	...	..	"	145	..	Two hours after high-protein meal (B.M.R.).
2–4	0.1	222	770.0	..	"	..	206¼	
2–6	1.1	133	...	..	"	62	..	No signs of hyperthyroidism.
2–11	0.8	181	...	..	"			
2–15	Neg.	250	480.0	1540	"	..	211½	
2–21	..	105	...	..	"			
2–25	Neg.	285	...	..	"			
3–5	Neg.	142	186.0					
3–10	Neg.	142	222.0	..	"	..	199	Lesions on arms and legs disappearing (Figs. 7, 8).
3–13	Neg.	100	...	..	"	..	200½	
3–16	Neg.	142	...	..	"			
3–20	Neg.	150	...	..	"			
3–24	Neg.	250	210.0	..	"	..	200	
3–30	1.1	333	...	..	40U t.i.d.	..	..	Diet: C. 135, P. 80, F. 180.
4–3	1.6	300	...	..	40U Q 4 H.			
4–8	1.8	285	660.0					
4–10	0.1	333	830.0	..	.....	..	..	Cholesterol ester, 236.
4–15	0.9	450	...	..	.....	..	..	Lesions are reappearing on arms and legs.
4–17	2.7	300						
4–24	..	365	...	..	.....	..	199½	
4–25	4.1	..	...	..	40U t.i.d.			
4–28	1.0	333	...	..	"			
5–8	1.2	400	300.0	..	"	..	198½	

Summary. A study of a patient with xanthoma diabeticorum associated with diabetes mellitus and acromegaly over a period of 4 years is reported with evidence to show that chronic cholesterolemia in man is not promptly followed by the development of arteriosclerosis.

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PHOTOMETRIC STUDIES OF VISUAL ADAPTATION IN RELATION TO MILD VITAMIN A DEFICIENCY IN ADULTS.*

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Essential hemeralopia, or night blindness, is the difficulty of adapting the faculty of vision to very faint illumination. The relation of vitamin A deficiency to hemeralopia has been clearly shown by the studies of Fridericia,[2] Holm,[3] Tansley,[8] and Wald,[9] and it is generally stated that hemeralopia is one of the earliest manifestations of vitamin A deficiency. In the last 3 years Jeans and Zentmire,[4] Park,[6] and Jeghers[5] in this country, Frandsen[1] in Denmark, and Snelling[7] in Canada have reported clinical studies of hemeralopia as a manifestation of vitamin A deficiency. Most of these authors used the Birch Hirschfeld type of photometer which has several objectionable features that make it difficult to establish satisfactory standards or to compare one author's data with those of another. Snelling goes so far as to say that he found the Birch Hirschfeld photometer unsatisfactory for the estimation of small variations in dark adaptation, and gives data on 12 healthy adult subjects who were tested on successive days. Over half of these subjects showed marked fluctuation from day to day, although there was no change in their usual routine. Recently, an improved photometer has been devised which measures dark adaptation in standard units of light intensity (millifoot candles), has a controlled and constant source of light for blanching and is so constructed that one can make readings quickly and with ease. Up to the present, only Jeans and Zentmire have reported a study using this instrument. Their report is concerned chiefly with the elaboration of a technique for its use. Although they state that several hundred subjects were tested, data are presented only on a group of 60 children. About as many of these subjects were found to have poor dark adaptation as were reported in previous studies using the Birch Hirschfeld photometer.

We have used this photometer recently to study the vitamin A nutrition of a group of adult patients attending our clinic and to determine the range of dark adaptation in normal adults.

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* This study was aided by a grant from the Division of Medical Sciences of the Rockefeller Foundation.

Methods. The subjects studied were 60 adult clinic patients, and 54 supposedly normal adults. All of the patients were ambulatory and had either functional or minor organic illnesses. Many of them gave histories of inadequate diets but none had outspoken signs of vitamin A deficiency save for an occasional one with a mild dermatosis. We regarded the group selected as fairly representative of our clinic patients. Ten of them are excluded from this report because of marked refractive errors (which we felt might possibly interfere with their dark adaptation), or because of ophthalmoscopically demonstrable eye lesions. The supposedly normal group was composed of doctors, technicians and clerical workers, all of whom were presumably healthy and were able to secure adequate diets.

After the original test, 22 of the patients were given 25,000 units of vitamin A daily by mouth in the form of halibut liver oil for 4 to 6 weeks and retested. Eleven of the supposedly normal subjects who showed poor adaptation were treated in the same way. For comparison, 10 from the same supposedly normal group with high original readings were also given supplementary vitamin A to determine whether their light perceptions could be improved or whether they were already at optimum levels. To determine the constancy of an individual's dark adaptation from day to day, 3 subjects from the normal group were tested on 10 successive days, 1 month after the completion of the above studies. No change was made in their usual routine or diets and they were not given supplementary vitamin A.

The instrument used is shown in Figure 1. Essentially it consists of a box in which are housed a source of strong light of constant intensity and a much weaker light, both separated from the eye piece by a metal screen which has 5 small perforations at its center in the form of the quincunx of the throw dice. The rays from the weak light source are transmitted through the perforations in this screen with diminishing intensity from left to right, and the amount of this light is controlled by a finely graded rheostat whose resistance is calibrated in terms of millifoot candles. Turning the rheostat control clockwise decreases the light intensity and the spots begin to fade. When the center spot fades completely the rheostat is turned counterclockwise until this spot just reappears, which is taken as the end point and recorded in millifoot candles. By means of a switch it is possible simultaneously to lower the screen from view and turn on the bright light for the purpose of exhausting visual purple.

The technique we employed in making the test is similar to that described by Jeans and Zentmire.[4] Testing requires a total of 23 minutes divided into 3 periods: 1, a 10-minute fore-period in the dark; 2, a 3-minute exposure to the bright light of the photometer; and, 3, a 10-minute recovery period in the dark. Frequent readings are made during the preliminary and recovery periods and the results can be shown best by means of a graph in which the photometer readings in millifoot candles are plotted against time in minutes (Fig. 2). The fore-period serves primarily to bring all subjects more nearly to an equal basis for the test. The mid-period represents the 3 minutes during which the subject's visual purple is exposed to the rays of a 100-watt lamp. The recovery period represents the most active stage of the regeneration of visual purple. The readings taken during the recovery period are the important ones and of these, the first, taken 20 seconds after blanching, is the most important. The smaller the reading in millifoot candles the better the dark adaptation. The curves of those with excellent dark adaptation approach a straight line and conversely those with the poorest adaptation depart farthest from a straight line graph. Readings late in the recovery period are also significant, and may indicate retarded or poor ultimate recovery.

Duplicate tests were made on many of the subjects and in the majority of the cases these readings were in satisfactory correspondence. The figures given represent an average when more than one determination was made.

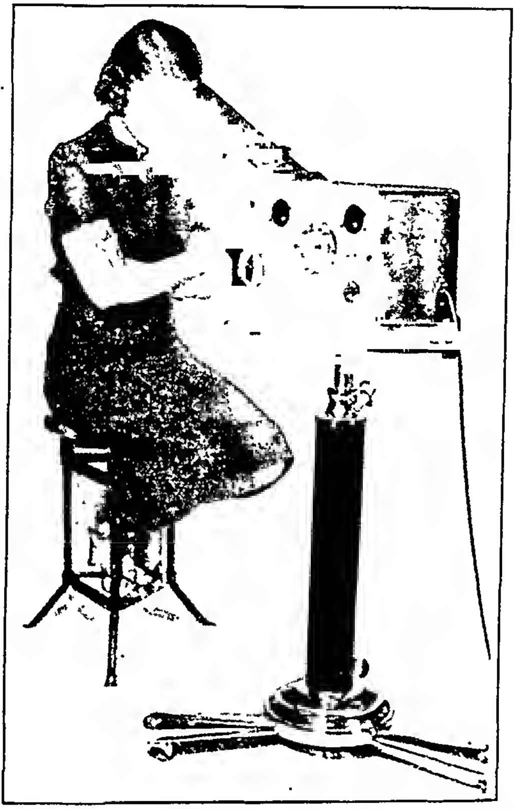

FIG. 1.—Photograph of photometer used in this study. (Biophotometer, manufactured by Frober-Faybor Company, Cleveland.)

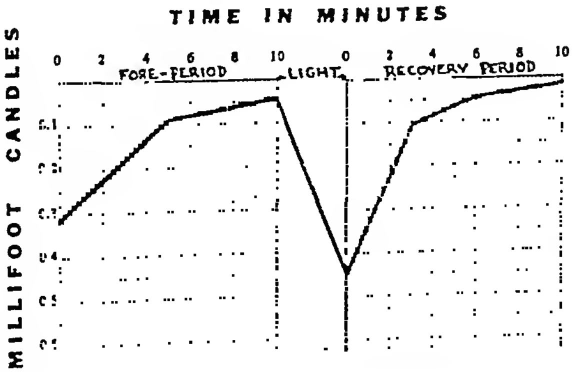

FIG. 2.—Typical graph of photometer readings in the three phases of the test period.

Results. The results of the examination of 54 supposedly normal subjects are given in Table 1. In Figure 3, we have represented the average readings for the whole group by means of a composite graph. The average value for the first reading in the recovery period was 0.50 millifoot candles, and the average value for the final reading was 0.02 millifoot candles. Also on this graph is shown the curve of the subject with the highest reading in the group and the curves of two low subjects. One of the latter was low because of a poor initial recovery reading; the other because of poor final recovery readings. In addition, we have plotted the initial recovery readings for each subject in the group, to give an idea of the spread of these

TABLE 1.—PHOTOMETER READINGS ON 54 "NORMAL" SUBJECTS.

			Fore period (10 minutes).			Recovery period (10 minutes).			
Subject.	Age.	Sex.	1 mfc.*	2 mfc.	3 mfc.	† 1 mfc.	2 mfc.	3 mfc.	4 mfc.
1 G. H.	26	F	0.660	0.295	0.123	0.900	0.258	0.080	0.067
2 A. M.	34	F	.565	.210	.099	1.875	.370	.080	.032
3 M. C.	27	M	.106	.025	.010	.368	.027	.014	.007
4 H. F.	33	F	.080	.018	.008	.390	.038	.016	.010
5 M. G.	26	F	.172	.021	.010	.204	.058	.019	.006
6 V. T.	25	F	.690	.105	.058	.580	.080	.029	.029
7 R. K.	41	M	.193	.028	.010	.130	.016	.006	.004
8 M. T.	38	F	.225	.043	.017	.305	.058	.016	.010
9 F. L.	25	F	.148	.015	.008	.142	.018	.010	006
10 L. T.	28	F	.097	.029	.022	.260	.063	.024	.008
11 J. Y.	42	M	.800	.158	.121	.700	.135	.106	.029
12 E. W.	29	F	.249	.063	.041	.472	.071	.081	.010
13 P. Z.	24	F	.240	.047	.022	.180	.041	.010	.010
14 S. C.	26	M	.328	.017	.007	.289	.063	.014	.008
15 H. K.	33	F	.380	.076	.044	.195	.026	.012	.007
16 M. K.	26	F	.440	.135	.042	.545	.145	.050	.025
17 M. R.	34	F	.063	.038	.014	.180	.035	.032	.014
18 E. B.	38	M	.260	.044	.015	.455	.055	.014	.010
19 T. R.	30	M	.395	.072	.035	.618	.118	.044	.024
20 A. N.	40	F	.129	.022	.019	.350	.030	.008	.006
21 E. W.	38	F	.216	.136	.029	.350	.160	.031	.009
22 T. B.	29	M	.076	.018	.008	.240	.047	.011	.009
23 A. M.	27	M	.210	.023	.010	.328	.078	.014	.005
24 E. J.	30	M	.445	.181	.104	.840	.132	.042	.014
25 S. W.	37	F	.341	.151	.039	.410	.126	.047	.035
26 J. V.	40	M	.240	.047	.019	.410	.092	.019	.014
27 F. S.	26	F	.592	.247	.265	.860	.260	.158	.118
28 A. B.	23	F	.447	.076	.042	.660	.154	.038	.016
29 T. H.	45	M	.180	.190	.092	.580	.195	.063	.038
30 J. H.	26	M	.195	.065	.024	.330	.026	.017	.010
31 M. M.	34	M	.240	.015	.007	.240	.046	.014	.008
32 L. S.	32	F	.187	.026	.006	.630	.018	.008	.012
33 S. H.	30	F	.237	.111	.026	.630	.105	.050	.027
34 R. D.	46	F	.440	.158	.058	.635	.238	.083	.049
35 K. M.	37	M	.315	.100	.024	.216	.030	.049	.018
36 H. K.	20	F	.450	.110	.035	.770	.191	.062	.041
37 H. W.	38	M	.240	.017	.015	.410	.069	.019	.007
38 A. C.	34	F	.340	.072	.017	.525	.055	.030	.011
39 F. L.	24	M	.136	.026	.010	.290	.052	.010	.008
40 W. C.	22	M	.240	.018	.015	.350	.019	.010	.004
41 V. Y.	17	F	.160	.063	.015	.380	.069	.015	.010
42 L. D.	22	M	.204	.107	.014	.840	.100	.041	.044
43 B. B.	24	M	.100	.024	.007	.520	.084	.018	.006
44 H. S.	26	M	.470	.096	.022	.380	.047	.016	.014
45 J. W.	37	F	.380	.216	.069	1.100	.315	.122	.058
46 J. W.	26	M	.350	.110	.092	.380	.160	.260	.069
47 M. M.	29	F	.187	.044	.035	.180	.047	.014	.024
48 J. E.	28	M	.069	.031	.008	.580	.026	.014	.006
49 E. G.	21	M	.440	.030	.020	.690	.063	.019	.005
50 B. K.	36	F	.630	.290	.136	1.000	.260	.216	.110
51 E. D.	22	F	.290	.084	.136	.470	.170	.058	.019
52 F. L.	29	F	.315	.044	.019	.350	.069	.016	.009
53 D. O.	25	M	.580	.136	.052	.380	.069	.022	.019
54 F. E.	23	M	...	...	.014	.800	.084	.017	.007

* Millifoot candles.

† Blanching (3 minutes).

values. Though some were low, 83% of them fell above 0.70 millifoot candles in their initial recovery reading.

Individual readings for the 50 clinic patients are shown in Table 2. The average readings for this group are shown by means of a composite curve in Figure 4, and also the initial recovery reading for each subject. Here the average value for the initial recovery reading was 0.88 millifoot candles and that of the final readings was 0.05 millifoot candles. There is considerably more spread of the initial recovery readings than in the normal group and 50% of the subjects fall below the 0.70 millifoot candle value.

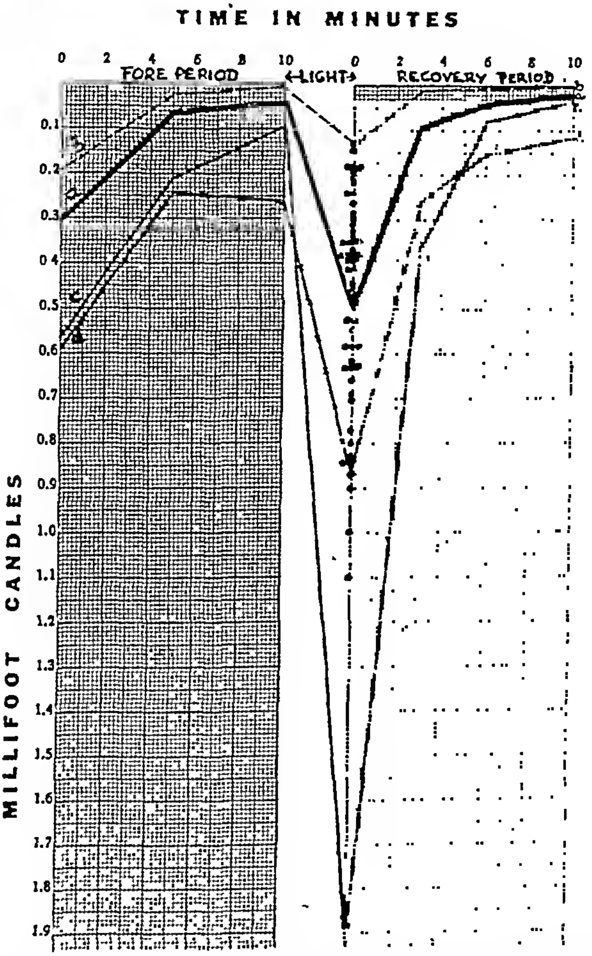

FIG. 3.—Graph of "normal" subjects: *a*, composite curve for 54 normals; *b*, highest subject in group; *c*, subject showing poorest initial recovery reading; *d*, subject showing poorest final recovery. The dots represent the initial recovery readings for each individual in the group.

The results with the 22 clinic patients who had low original readings and were given vitamin A for 4 to 6 weeks are shown in Table 3.

All but one of these patients (Case 22) showed definite improvement, most evident in the initial recovery reading. Composite curves representing the average readings of this group before and after treatment are shown in Figure 5. It is noteworthy that the average initial recovery reading after treatment was 0.59 millifoot candles.

TABLE 2.—PHOTOMETER READINGS ON 50 PATIENTS.

			Fore period (10 minutes).			Recovery period (10 minutes).			
Subject.	Age.	Sex.	1 mfc.*	2 mfc.	3 mfc.	† 1 mfc.	2 mfc.	3 mfc.	4 mfc.
1 O. H.	30	F	0.240	0.058	0.038	0.880	0.100	0.084	0.029
2 M. H.	44	F	1.250	.655	.226	1.530	.580	.285	.069
3 B. B.	60	F	.457	.055	.035	.930	.150	.042	.031
4 C. M.	52	F	.260	.072	.024	.520	.136	.031	.018
5 F. R.	44	F	.970	.233	.067	1.080	.243	.095	.039
6 H. B.	35	F	.122	.031	.010	.440	.052	.019	.014
7 H. B.	24	F	.260	.105	.031	.580	.142	.063	.031
8 P. W.	58	M	.890	.302	.141	.920	.350	.086	.050
9 P. G.	20	M	.076	.065	.016	.260	.084	.024	.011
10 R. M.	30	M	.350	.058	.018	.365	.076	.023	.010
11 L. L.	52	F	.500	.170	.092	1.340	.520	.132	.082
12 F. T.	41	F	.440	.350	.170	1.000	.690	.290	.160
13 E. W.	32	F	.975	.259	.235	1.480	.815	.405	.212
14 M. S.	19	F	.635	.048	.035	.575	.098	.044	.010
15 C. G.	23	F	.228	.024	.003	.417	.066	.016	.007
16 M. L.	40	F	.315	.031	.018	.690	.069	.015	.008
17 A. B.	19	F	.260	.228	.024	.550	.160	.060	.045
18 R. M.	55	F	1.250	.690	.420	2.810	.535	.294	.256
19 W. P.	20	M	.195	.110	.031	.365	.092	.030	.014
20 N. J.	40	F	.550	.260	.026	1.100	.122	.076	.063
21 L. P.	29	F	.100	.015	.007	.350	.044	.013	.005
22 S. A.	45	F	.180	.052	.014	1.100	.216	.058	.017
23 C. S.	32	F	.240	.024	.007	.630	.122	.052	.010
24 J. V.	53	M	.136	.148	.024	.580	.084	.024	.007
25 W. K.	52	M	.660	.235	.054	1.010	.129	.066	.035
26 M. L.	49	M	.840	.380	.092	.690	.195	.055	.038
27 P. H.	20	M	.580	.217	.042	.760	.220	.090	.049
28 J. L.	23	M	.315	.031	.018	.315	.047	.008	.004
29 G. L.	37	M	.580	.100	.038	.315	.058	.024	.008
30 S. T.	21	F	.440	.100	.038	.580	.148	.047	.026
31 G. S.	22	F	.520	.180	.022	.690	.160	.031	.019
32 C. J.	29	M	1.360	.880	.122	1.220	.350	.148	.084
33 S. D.	50	F	1.800	.580	.122	1.360	.180	.063	.012
34 L. R.	38	M	.216	.015	.038	.840	.069	.031	.011
35 T. E.	32	M	1.220	.760	.260	1.480	.350	.216	.213
36 A. P.	27	F	.760	.260	.216	1.360	.290	.160	.080
37 L. L.	33	M	.410	.029	.019	.580	.110	.030	.014
38 J. T.	66	M	.690	.122	.027	1.480	.290	.063	.010
39 G. W.	46	M	.380	.122	.069	.920	.290	.076	.058
40 O. B.	19	M	.122	.010	.006	.240	.019	.006	.003
41 M. P.	17	F	.440	.069	.022	.840	.315	.084	.019
42 H. W.	26	F	.440	.100	.029	.520	.122	.044	.015
43 T. R.	42	M	1.360	.520	.228	1.360	.470	.260	.110
44 E. H.	19	M	.160	.047	.010	.440	.029	.007	.003
45 M. Y.	63	F	1.000	.350	.122	2.500	.240	.116	.047
46 E. C.	21	F	.290	.187	.052	.520	.216	.092	.031
47 R. M.	35	F	1.480	.470	.160	1.800	.180	.148	.122
48 R. N.	32	M	.260	.026	.014	.470	.063	.014	.005
49 K. B.	24	M	.840	.260	.069	.760	.260	.047	.110
50 I. B.	37	F	.315	.122	.026	.380	.084	.038	.014

* Millifoot candles.

† Blanching (3 minutes).

The results with 11 normal subjects who had low original readings and were given supplementary vitamin A are shown in Table 4, before and after treatment. Composite curves of these findings are shown in Figure 6. All of these subjects showed definite improvement, requiring an average of 0.45 millifoot candles less of light for the initial recovery readings after treatment.

The composite curves before and after treatment of the 10 subjects with high readings from the same group are also shown in Figure 6, while their individual readings are given in Table 5. Here the changes were very slight, indicating that these subjects were

TABLE 3.—PHOTOMETER READINGS ON 22 PATIENTS WITH LOW ORIGINAL READINGS, BEFORE AND AFTER TAKING VITAMIN A SUPPLEMENT.

				Before vitamin A.							After vitamin A.						
				Fore period.			Recovery period.				Fore period.			Recovery period.			
	Subject.	Age.	Sex.	1 mfc.*	2 mfc.	3 mfc.	1 mfc.	2 mfc.	3 mfc.	4 mfc.	1 mfc.	2 mfc.	3 mfc.	1 mfc.	2 mfc.	3 mfc.	4 mfc.
1	M. H.	44	F	1.250	0.655	0.226	1.530	0.580	0.285	0.068	0.950	0.450	0.135	0.800	0.410	0.157	0.048
2	F. R.	44	F	.970	.233	.067	1.080	.243	.095	.039	.840	.350	.092	.760	.240	.100	.018
3	P. W.	58	M	.890	.302	.141	.920	.350	.086	.050	.690	.100	.031	.440	.084	.044	.018
4	L. L.	52	F	.500	.171	.092	1.340	.520	.133	.082	.840	.440	.100	.350	.240	.110	.069
5	E. W.	32	F	.975	.259	.235	1.480	.815	.405	.212	.760	.160	.058	.470	.195	.076	.038
6	M. S.	19	F	.635	.048	.035	.575	.098	.044	.010	.380	.110	.028	.315	.100	.024	.006
7	S. A.	45	F	.180	.052	.014	1.100	.216	.058	.017	1.100	.136	.029	.630	.160	.063	.026
8	W. K.	52	M	.660	.235	.054	1.010	.129	.066	.035	.840	.160	.052	.690	.033	.038	.029
9	M. L.	49	M	.840	.380	.092	.690	.195	.055	.038	.690	.315	.136	.470	.180	.076	.047
10	P. H.	20	M	.580	.217	.042	.760	.220	.090	.049	.580	.260	.110	.630	.148	.084	.029
11	S. T.	21	F	.440	.100	.038	.580	.148	.047	.026	.690	.195	.063	.240	.100	.029	.029
12	G. S.	22	F	.520	.180	.022	.690	.160	.032	.019	.260	.058	.024	.315	.063	.026	.010
13	C. J.	29	M	1.360	.880	.122	1.220	.350	.148	.084	.760	.440	.110	.690	.315	.100	.058
14	S. D.	50	F	1.800	.580	.122	1.360	.180	.063	.012	.470	.148	.047	.690	.330	.100	.058
15	T. E.	32	M	1.220	.760	.260	1.480	.350	.216	.213	.690	.470	.520	.800	.350	.440	.110
16	A. P.	27	F	.760	.260	.216	1.360	.290	.160	.080	.440	.084	.019	.440	.038	.018	.018
17	J. T.	66	M	.690	.122	.027	1.480	.290	.063	.010	1.220	.136	.024	.520	.076	.035	.008
18	T. R.	42	M	1.360	.520	.228	1.360	.470	.260	.110	1.100	.180	.100	.760	.290	.092	.058
19	M. Y.	63	F	1.000	.350	.122	2.500	.240	.116	.047	1.220	.350	.216	1.600	.470	.136	.084
20	K. B.	24	M	.840	.260	.069	.760	.260	.047	.110	.630	.047	.018	.255	.029	.008	.003
21	M. P.	17	F	.440	.069	.022	.840	.315	.084	.019	.580	.160	.031	.290	.240	.038	.022
22	O. H.	30	F	.240	.058	.038	.880	.100	.084	.029	.470	.110	.024	.840	.260	.069	.018

* Millifoot candles.

already at about their optimum dark adaptation, and presumably in an optimum state of vitamin A nutrition.

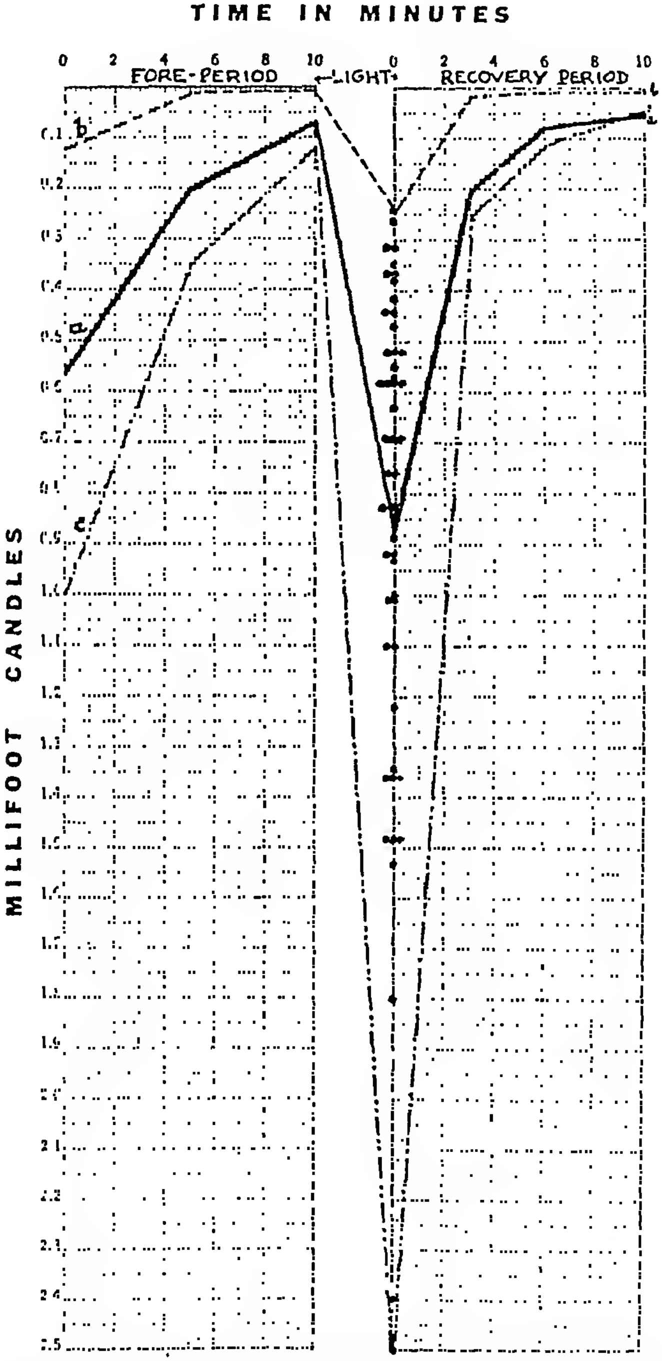

FIG. 4.—Graph of patients: *a*, composite curve for 50 clinic patients; *b*, highest subject in group; *c*, lowest subject in group. The dots represent the initial recovery reading for each subject in the group.

The initial recovery and the final recovery readings for the 3 normal subjects tested on 10 successive days are shown in Table 6.

TABLE 4.—PHOTOMETER READINGS FOR 11 LOW "NORMAL" SUBJECTS BEFORE AND AFTER TAKING VITAMIN A SUPPLEMENT.

		Before vitamin A							After vitamin A.						
		Fore period.			Recovery period				Fore period.			Recovery period.			
		1 mfc.*	2 mfc.	3 mfc.	1 mfc.	2 mfc.	3 mfc.	4 mfc.	1 mfc.	2 mfc.	3 mfc.	1 mfc	2 mfc.	3 mfc.	4 mfc
1	G. H.	0 660	0 295	0 123	0 900	0 258	0 080	0 067	0 170	0 122	0 035	0 315	0 100	0 022	0 008
2	A. M.	565	210	099	1 875	370	080	032	315	014	.006	290	084	009	005
3	J. Y.	.800	158	121	700	135	.106	028	760	076	.019	580	076	029	008
4	T. R.	395	072	035	617	118	013	024	.308	082	021	360	084	046	025
5	C. J.	115	181	104	840	132	012	014	350	260	.260	630	380	290	008
6	P. S.	592	217	265	860	200	158	118	440	350	240	690	350	205	122
7	A. B.	117	076	042	.660	154	038	.016	300	076	026	350	100	024	016
8	R. D.	110	158	058	640	238	083	049	580	180	047	260	122	069	026
9	H. K.	150	110	035	770	191	062	041	470	092	031	470	100	.063	018
10	L. D.	201	107	014	840	100	041	044	260	019	.009	315 -	069	012	006
11	B. K.	630	290	136	1 000	260	216	110	760	260	063	470	136	092	047

* Millifoot candles.

TABLE 5.—PHOTOMETER READINGS FOR 10 HIGH "NORMAL" SUBJECTS BEFORE AND AFTER TAKING VITAMIN A SUPPLEMENT.

		Before vitamin A.							After vitamin A.						
		Fore period			Recovery period				Fore period			Recovery period			
Subject.		1 mfc.*	2 mfc.	3 mfc	1 mfc.	2 mfc.	3 mfc	4 mfc.	1 mfc	2 mfc.	3 mfc	1 mfc.	2 mfc.	3 mfc.	4 mfc
1	M. C.	0 106	0 025	0 010	0 368	0 026	0 014	0 007	0 237	0 054	0 023	0 270	0 057	0 035	0 004
2	H. F.	.080	017	008	390	038	016	.010	190	025	009	310	053	019	007
3	M. G.	.172	.021	010	204	058	019	006	070	014	003	360	.102	032	013
4	M. T.	225	.013	.017	305	058	016	010	118	029	006	260	038	014	006
5	E. W.	219	.063	.011	.472	071	.081	010	410	.044	016	380	035	026	009
6	S. C.	328	017	.007	289	063	011	008	122	.019	008	290	024	009	004
7	M. K.	110	.135	042	546	115	.050	.025	.290	115	020	360	091	039	.011
8	A. M.	.210	.023	010	328	078	014	.005	.470	063	008	216	058	016	008
9	S. W.	.311	151	039	410	126	016	.035	.365	.063	018	290	115	.014	015
10	A. C.	.310	.072	.017	.526	055	.030	.011	.315	.063	.031	365	.063	.038	.016

* Millifoot candles.

On the whole, these readings show only slight variation from day to day, and fail to show the marked inconsistencies reported by Snelling, who used the Birch Hirschfeld photometer.

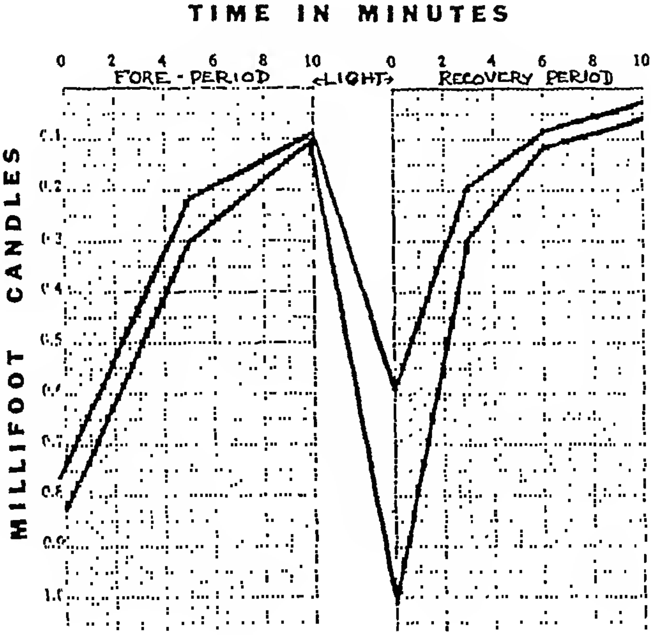

FIG. 5.—Composite curves for 22 clinic patients before and after treatment with vitamin A supplement (upper curve represents average readings after treatment).

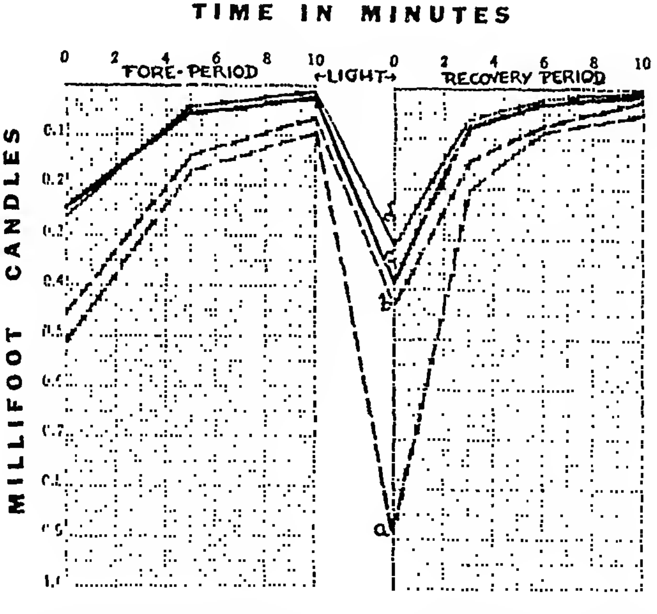

FIG. 6.—"Normal" subjects given vitamin A supplement. *a*, Curve for 11 "normals" with low readings, before taking vitamin A; *b*, same subjects, after taking vitamin A; *c*, curve for 10 "normals" with high readings, before taking vitamin A; *d*, same subjects, after taking vitamin A.

TABLE 6.—SUCCESSIVE DAILY READINGS ON 3 NORMAL SUBJECTS.

	Subject 1.		Subject 2.		Subject 3.	
Day.	Initial recovery reading. mfc.*	Final reading. mfc.	Initial recovery reading. mfc.	Final reading. mfc.	Initial recovery reading. mfc.	Final reading. mfc.
1	0.240	0.008	0.315	0.008	0.470	0.009
2	.240	.003	.216	.006	.260	.009
3	.180	.010	.290	.006	.260	.010
4	.275	.006	.240	.007	.275	.010
5	.290	.006	.290	.009	.380	.012
6	.260	.005	.260	.006	.260	.010
7	.275	.005	.260	.006	.260	.008
8	.315	.007	.260	.006	.350	.006
9	.275	.007	.260	.007	.290	.006
10	.260	.007	.240	.007	.290	.007
Average	.261	.006	.263	.007	.309	.009

* Millifoot candles.

Discussion. Our data on the supposedly normal group show some variations in the light perceptions of these subjects and some obviously have abnormally low readings. A check on the diet habits of these low subjects was not particularly revealing, and to explain these low readings one is forced to consider such factors as absorption and individual variations in vitamin A requirement. Inasmuch as 83% of these subjects had initial recovery readings of 0.70 millifoot candles or less, and all of those with poorer dark adaptation were brought within this range by treatment, it seems reasonable to regard this point as the limit of normal for the present. This conclusion is supported by the fact that the average initial recovery reading of the clinic patient group was below this value and was raised to within this range by treatment, and by the fact that normal subjects with initial readings within this range were but little improved by additional amounts of vitamin A. Such a standard agrees fairly well with that suggested by Jeans and Zentmire, who placed the limit of normal at 0.60 millifoot candles, for the initial recovery reading.

By such standards we find that 50% of a representative group of our adult clinic patients had readings below 0.70 millifoot candles after blanching. Inasmuch as all of these (including those with very low readings) were improved, and all but 6 improved to above 0.70 millifoot candles after treatment, it appears that about half of our patients were in a state of mild vitamin A deficiency as indicated by photometric studies. The constancy of the daily readings in the 3 normal subjects indicates that the photometer used in these studies apparently is more reliable than the Birch Hirschfeld for making dark adaptation studies in adults.

Conclusions.—1. We found the photometer and the technique described by Jeans and Zentmire quite satisfactory for making photometric studies in adults.

2. From a study of 54 healthy adults, we propose an initial recovery reading of 0.70 millifoot candles as a tentative value for the normal limit of dark adaptation.

3. Several subjects with relatively poor dark adaptation were found in the supposedly normal group and all were improved by treatment with vitamin A.

4. By the standards arrived at in this study about 50% of a group of adult ambulatory out-patients were found to have poor dark adaptation, indicating mild vitamin A deficiency. The great majority of these patients who received treatment showed definite improvement in dark adaptation.

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POST-TRAUMATIC INTERNAL HYDROCEPHALUS.

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This report is based upon a study of 4 cases of acquired chronic internal hydrocephalus. In each there was a history of severe head injury antedating the symptoms of the disease. Postmortem examination disclosed a chronic productive leptomeningitis in the region of the roof of the fourth ventricle with hemosiderin pigmentation of the scar tissue and dilatation of all ventricles.

In 1914, Dandy and Blackfan,[3] in a report of their observations on internal hydrocephalus, stated that "the production of hydrocephalus by trauma is very difficult to prove. We have seen 1 case (not reported here) in which the father, who was a physician, insisted that the onset of the disease dated from the severe fall." Horrax,[9] in 1924, in a report of 33 cases of "generalized cisternal arachnoiditis simulating cerebellar tumor," included the case of a female, aged 28 years, who fell on the ice and "was stunned for a few minutes." Subsequently she developed internal hydrocephalus and 5 years following the injury was operated upon with the removal of scar tissue from the region of the roof of the fourth ventricle. She made a satisfactory recovery. Horrax did not discuss the matter of post-traumatic hydrocephalus and did not say whether he considered the trauma in the above cited case to be significant or not. In 1925, Foerster[4] reported the case of a child, aged 11, who developed an internal hydrocephalus following a head injury. At operation there was a subcerebellar "arachnoid cyst," the removal of the lower wall of which resulted in cure.

A causal relationship between birth injury and internal hydrocephalus has been observed more frequently than has the causal relationship between postnatal head injury and hydrocephalus.

Fraser and Dott[6] made the unequivocal statement that "we possess very definite evidence that intracranial hemorrhage produced at birth is liable to be followed by hydrocephalus if the location of the hemorrhage is subtentorial." They cited 7 cases of intracranial birth hemorrhage followed by the development of internal hydrocephalus in which subsequent operation revealed an obstructive "hemorrhagic effusion in the membranes," in the region of the fourth ventricle.

In a critical investigation of the subject, Ford[5] concluded that following birth injury "it is possible that the aqueduct of Sylvius may be plugged by blood clot or bits of necrotic brain tissue which become organized and a progressive hydrocephalus ensues. In 6 cases out of 200 it is probable but not certain that this actually took place." Jacobs[10] reported a case of progressive acquired internal hydrocephalus following birth injury with subarachnoid hemorrhage which was cured by the removal of subtentorial "yellow adhesions" which had occluded the foramina of Magendie and Luschka.

The roentgenologic findings in persons showing delayed neurologic disturbances after head injury indicate that post-traumatic hydrocephalus is more common than the above case reports would indicate. Friedman[7] reported the results of encephalographic examinations in 20 cases of "so-called traumatic neuroses following serious injury to the skull." The head injuries had been sustained from between 8 days and 12 years prior to the encephalographic examination and in 80% of them internal hydrocephalus was found to be present. Kennedy[11] regarded the finding of internal hydrocephalus as one of the important criteria for determining whether or not organic disability had followed a head injury.

There appears then to be a disparity between the clinical pathologic studies (as indicated by case reports) and the encephalographic evidence of Friedman as to the frequency of internal hydrocephalus following head injury. If in some instances there is a definite cause and effect relationship between head injury and chronic progressive internal hydrocephalus the recognition of that relationship is of obvious importance in legal medicine. Furthermore, if the cause of the hydrocephalus is commonly the same as that described by Jacobs, the condition is, on anatomic grounds, amenable to cure by surgical means.

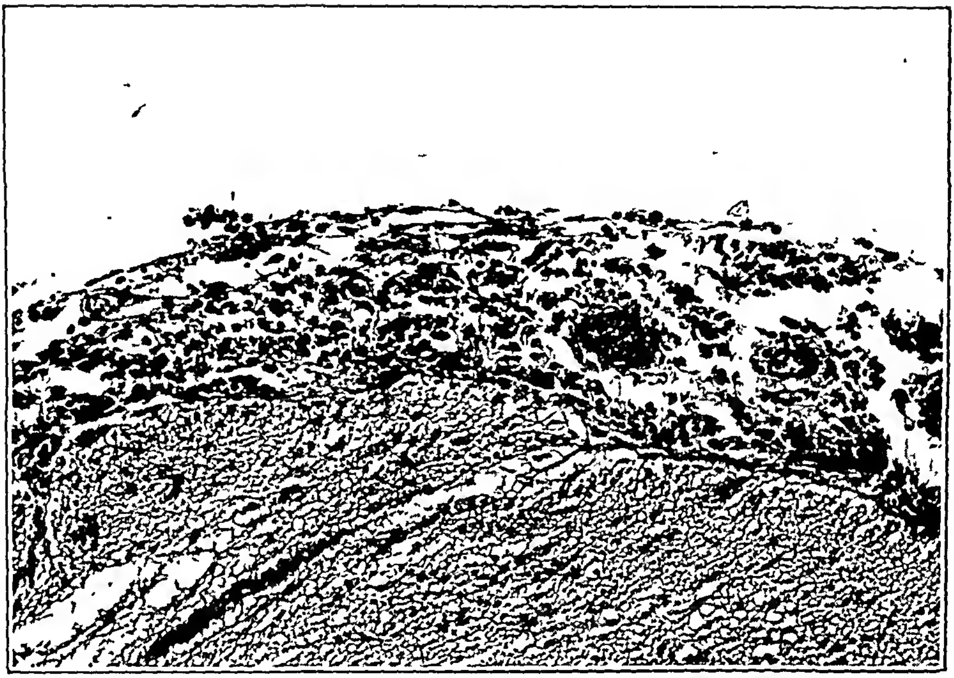

FIG. 1.—Large hemosiderin-containing phagocytes in thickened leptomeninges over pons in Case 5413. (X 220.)

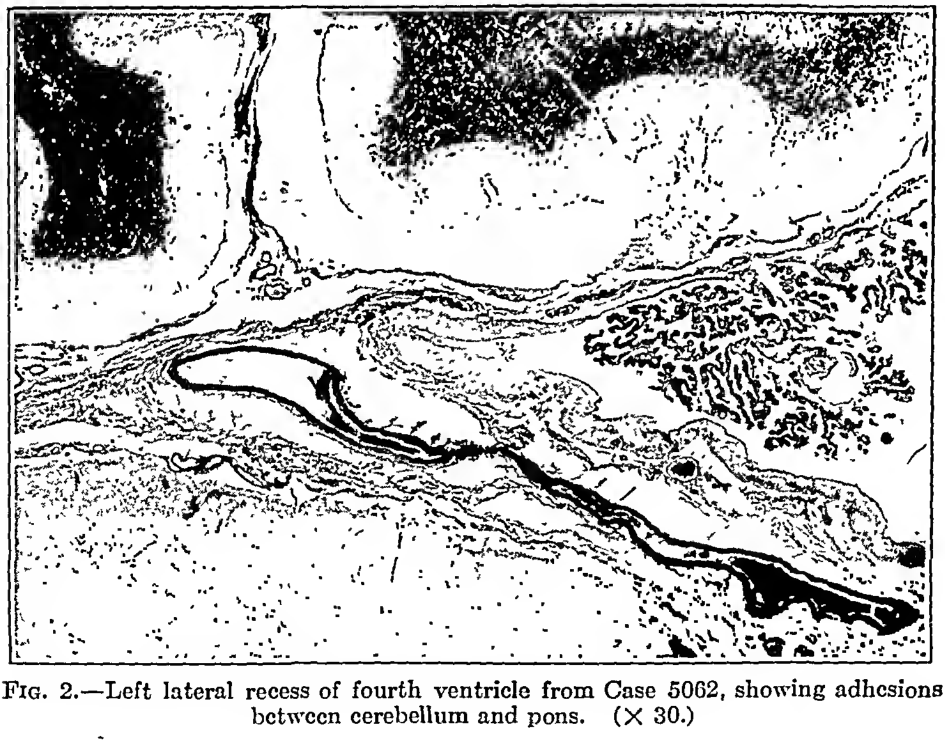

FIG. 2.—Left lateral recess of fourth ventricle from Case 5062, showing adhesions between cerebellum and pons. (X 30.)

The pertinent data concerning the 4 cases included in this report are as follows:

Case Reports. Case 5062.—The patient was a white female of 4 years, who sustained a skull fracture as a result of being struck by an automobile. There was immediate loss of consciousness, with profuse bleeding from the nose and ears. Upon discharge from the hospital, there was no clinical evidence of organic disease of the brain. No medical record was available as to her subsequent course. About 4 months after the injury she was reported to have had convulsions which increased in frequency and severity. She became stuporous and died at home without further medical observation. Death occurred 6½ months following the injury.

Postmortem examination disclosed a pronounced internal hydrocephalus involving all ventricles and including the lateral recesses of the fourth ventricle. There was no enlargement of the head. There was a chronic basilar leptomeningitis in the region of the roof of the fourth ventricle with adhesions between the cerebellum and the pons. These adhesions were sparsely infiltrated by lymphocytes and hemosiderin-containing phagocytes. There was disseminated focal hemosiderin pigmentation of the leptomeninges.

Case 5309.—The patient was a white male who sustained a cerebral concussion at the age of 16 as the result of being struck on the head by a baseball. There was loss of consciousness for a short duration but no immediate signs or symptoms of residual cerebral damage. Shortly after the injury, changes in behavior were noted and he became intractable and asocial. Approximately 8 years following the injury, periodic syncope developed associated with weakness and periods of disorientation. There was a rapid deterioration during the last 6 weeks of life with terminal vomiting, cervical rigidity, hyperactive reflexes, a sense of strangling and papilledema.

Postmortem examination disclosed dilatation of all ventricles but most pronounced of the lateral and third. There were dense hemosiderin-containing adhesions between pons and cerebellum. There were organized subependymal hematomas in the left lateral ventricle. The brain weighed 1900 gm.

Case 5413.—The patient was a white female child who sustained an intracranial hemorrhage during a difficult breech delivery. There was paralysis of all extremities and blindness of both eyes. Hydrocephalus was not thought to be present at the time of birth. At the age of 2½ months it was thought that the head was enlarging and an encephalogram disclosed hydrocephalus to be present. At the age of 3½ years periodic convulsions occurred and these persisted at irregular intervals until death. The terminal illness began with an acute otitis media followed by an acute meningo-encephalitis. The patient was 8 years old when she died.

Postmortem examination disclosed internal hydrocephalus with dilatation of all ventricles and marked enlargement of the head. There was a chronic productive basilar leptomeningitis with adhesions containing hemosiderin between pons and cerebellum. There was disseminated focal hemosiderin pigmentation of the leptomeninges. There was an acute otitis media, an acute sphenoidal sinusitis and an acute exudative meningo-encephalitis.

Case 5499.—The patient was a white male of 28 years who fell and struck his head violently with a temporary loss of consciousness. There were no immediate neurologic signs of residual cerebral injury. Two weeks following the injury, headaches and vomiting developed, which increased in severity and frequency for the next 2½ months. Following the diagnosis of internal hydrocephalus, based upon encephalographic studies, an operation was performed at which time adhesions in the region of the roof of the fourth ventricle were removed. There was temporary improvement but within a few weeks there was a recurrence of symptoms. Death occurred 3½ months after the head injury.

Postmortem examination disclosed dilatation of all ventricles resulting from a chronic productive basillary leptomeningitis in the region of the roof of the fourth ventricle. There were adhesions between the pons and the cerebellum. The adhesions were infiltrated by lymphocytes and large hemosiderin-containing phagocytes. There was some perivascular lymphocytic infiltration in the brain tissue beneath the thickened leptomeninges.

Discussion. A comparison of these 4 patients showed them to possess several clinical and pathologic features in common. All had a definite history of trauma followed by a period of unconsciousness, although only 1 patient (Case 5062) was known to have had a fractured skull. There was a latent period of variable duration between the accident and the onset of symptoms indicative of the development of internal hydrocephalus. The intervals between head injury and death varied from 3½ months to 8 years. The outstanding symptoms were stiff neck, lethargy, headache and vomiting. The terminal period of the disease was characterized by a rapid increase in the severity of all symptoms and included a rising pulse rate, respiratory embarrassment, papilledema, an increased spinal fluid pressure and the development of abnormal reflexes. The cranial nerves usually remained unaffected. One patient (Case 5499) was benefited temporarily by repeated spinal taps and the injection of air beneath the spinal dura.

The postmortem findings were similar in each case. There was partial or complete fusion of the pia arachnoid in the region of the fourth ventricle by fibrous adhesions which were infiltrated by lymphocytes and large hemosiderin-containing macrophages (Fig. 1). These adhesions obliterated the space between cerebellum and pons so that the roof of the fourth ventricle could be exposed only by sharp dissection. Although the ventricular system was not injected, it was apparent that there was obstruction of the foramina of Luschka and Magendie. In all 4, the Sylvian aqueduct was dilated and shortened, and all ventricles were enlarged. In Case 5062 the lateral recesses of the fourth ventricle were dilated (Fig. 2). In Case 5413 an acute meningo-encephalitis secondary to otitis media developed terminally.

Pathogenesis. These cases are examples of acquired internal hydrocephalus apparently due to adhesions in the region of the fourth ventricle. According to Dandy[2] these are the most common causes of this type of hydrocephalus; he has pointed out that "an obstruction in the cisterna under the medulla, pons or mesencephalon (that is, at any point between the foramina of Luschka and the cisterna interpeduncularis) will produce a stasis of fluid up to the point of an obstruction just as effectively as would a block at the aqueduct of Sylvius or at the foramina of Luschka and Magendie." It is true, however, that the unequivocal proof of the production of obstructive adhesions by trauma is difficult to establish. No matter what the sequence of a severe head injury, the development of signs and symptoms of increased intracerebral pressure and the pathologic demonstration of the kind and location of the obstruction may be, it cannot be proved that the trauma was anything more than a coincidence and that the adhesions did not result from a healed infectious leptomeningitis.

The pathogenesis of such lesions must be considered on a basis of probability only. The great variation in the manner in which extravasated blood is absorbed or organized is well known and to Aschoff's[1] statement that "das Schicksal des vergossenen Blutes ist ganz verschieden nach der Localization" might be added "und auch abhängend von der Grösse des Hämatoms." Merkel[12] has called attention to the tendency of extravasated subarachnoid blood to gravitate to the base of the skull beneath the cerebellar tentorium and over the medulla. Ford[5] has described the immediate inflammatory response to subarachnoid bleeding as indicated by fever, leukocytosis and increase in white blood cells in the cerebral spinal fluid. Winkelman and Eckel[13] observed a fixed tissue reaction in the leptomeninges in the form of fibroblastic proliferation following subarachnoid hemorrhage. Although both Hashiguchi[8] (in dogs) and Wortis[14] (in cats) reported the frequent development of a slight degree of internal hydrocephalus following experimentally produced skull fractures in animals, neither of them described organizing subarachnoid hematomas. A crucial experiment would be the production of a subarachnoid hematoma in animals by the injection of homologous blood and a subsequent study of its absorption and organization. No published reports of such experiments have been found.

It seems probable that leptomeningeal adhesions may form as a result of the organization of a subarachnoid hematoma. The frequent occurrence of subarachnoid hemorrhage following severe head injury with or without skull fractures is well known (Winkelman and Eckel). In the 4 cases here reported the subjects were, so far as could be determined, normal prior to a severe head injury. Subsequently they developed an internal hydrocephalus which was found to be the result of obstructive leptomeningeal adhesions in the region of the fourth ventricle. The presence of intracellular and extracellular hemosiderin in these adhesions indicates that they resulted from the organization of a hematoma or of a hemorrhagic exudate. Since traumatic hemorrhage can be inferred to have occurred and since there was no history of an infectious leptomeningitis it seems reasonable to attribute the adhesions to the preceding head injury.

Summary. Four cases of head injury followed by chronic internal hydrocephalus have been described. So far as was known, the individuals were normal before the injury, which in every instance was sufficiently severe to have caused temporary loss of consciousness. Signs or symptoms of internal hydrocephalus developed from 2 weeks to 8 years after the injury and progressed with varying rapidity to death. Postmortem examination disclosed dilatation of all ventricles as a result of chronic obstructive leptomeningitis in the region of the roof of the fourth ventricle. The leptomeningeal adhesions contained hemosiderin and it was thought that they probably resulted from the organization of a subdural hematoma which formed as the result of a head injury.

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THE ASSIMILATION OF PROTEIN BY YOUNG CHILDREN WITH THE NEPHROTIC SYNDROME.

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Information concerning protein nutrition is needed to answer several questions concerning the behavior and treatment of so-called "lipoid nephrosis" and the nephrotic type of Bright's disease.

The practical question of the optimal diet for protein regeneration in nephrosis has been without experimental answer. Since Epstein[3] it has been customary to feed as much protein as possible, but it has never been shown whether the maximum intake causes the most rapid regeneration of protein in either the tissues or the blood plasma.

Conditions of Observation. Five children, all 4 years of age, with the nephrotic syndrome were observed continuously for a period of 54 days on diets differing in the protein content. Four were Caucasian and 1 (I. C.) was Chinese. Four (I. C., J. M., E. S., and J. T.) were observed simultaneously and the fifth (R. G.) was observed several months later. The diets were skillfully prepared and fed under the direction of Miss G. Drew. Four of the children were observed for a preliminary period while the routines for collection of specimens were being checked. During this period they were fed a diet of 1500 calories containing more fat than was fed later.

After the techniques of collection were satisfactorily worked out, the caloric intake was reduced to 1000 calories. It was originally planned to maintain the caloric intake at this level throughout the experiment, but in order to keep the children eating well it was necessary on the higher protein diets to increase this diet to 1200 calories in three cases. In 2 instances it was possible to feed the desired range of protein without increasing the caloric intake. The total period was divided into 7 shorter intervals of approximately a week each, and during each interval a different protein intake was given. The salt intake was restricted to about 1 gm. per day. The protein intake in 4 of the children varied from 0.6 gm. per kilo. of ideal (normal for height and age) body weight to 4.8 gm. per kilo. and was given in this order, and in the fifth child from 1.1 to 4.4 gm. per kilo. In the fifth child the diet was started with 2.2 gm. of protein per kilo. of ideal body weight and increased gradually to 4.4 gm. per kilo., then decreased to 1.7 gm., followed by 1.1 gm. This was done to observe after effects of the high-protein period. Analysis of the diets is shown in Table 1. The fat and carbohydrate contents in the 4 children's diet were both varied during the first 3 periods, including the preliminary period previously noted. During the last 3 periods the fat was kept constant and only the protein and carbohydrate varied; in the fifth child the fat and caloric content were constant. The greater part of the protein offered consisted of meat, chiefly beef. Eggs and vegetables in the order given provided the rest of the protein. Milk was only sparingly given, usually 100 cc. or less per day. At no time during the course of these observations was it necessary to resort to feeding prepared protein mixtures, such as casein or lactalbumin in milk, in order to bring the protein intake up to the desired level. In addition to the regular diet, which included fresh fruits and vegetables, the children were given 2 haliver oil capsules with viosterol and 5 gm. of fresh brewer's yeast daily. Fluid was given *ad lib.* throughout the period of observation. The children with 1 exception (I. C.) had good appetites and took the diets cheerfully and even avidly at all times. There were no illnesses during the period of observation, although 1 of the patients (J. M.) had an acute gastric upset, manifested by vomiting, during one morning when urea and creatinine were fed by mouth in the postabsorptive state. There was no diarrhea at any time nor any noticeable change in the character or frequency of the stools. Laxatives were not needed and were not used at any time during the period of observation. Detailed laboratory and clinical data are shown in Charts 1, 2, 3, 4 and 5. The children were allowed to carry on as much activity as was consonant with their physical condition. Through the efficient coöperation of the nursing staff under Miss E. Glantz, it was possible to collect without loss the daily urinary output of each child. There were no restraints nor metabolic cribs used.

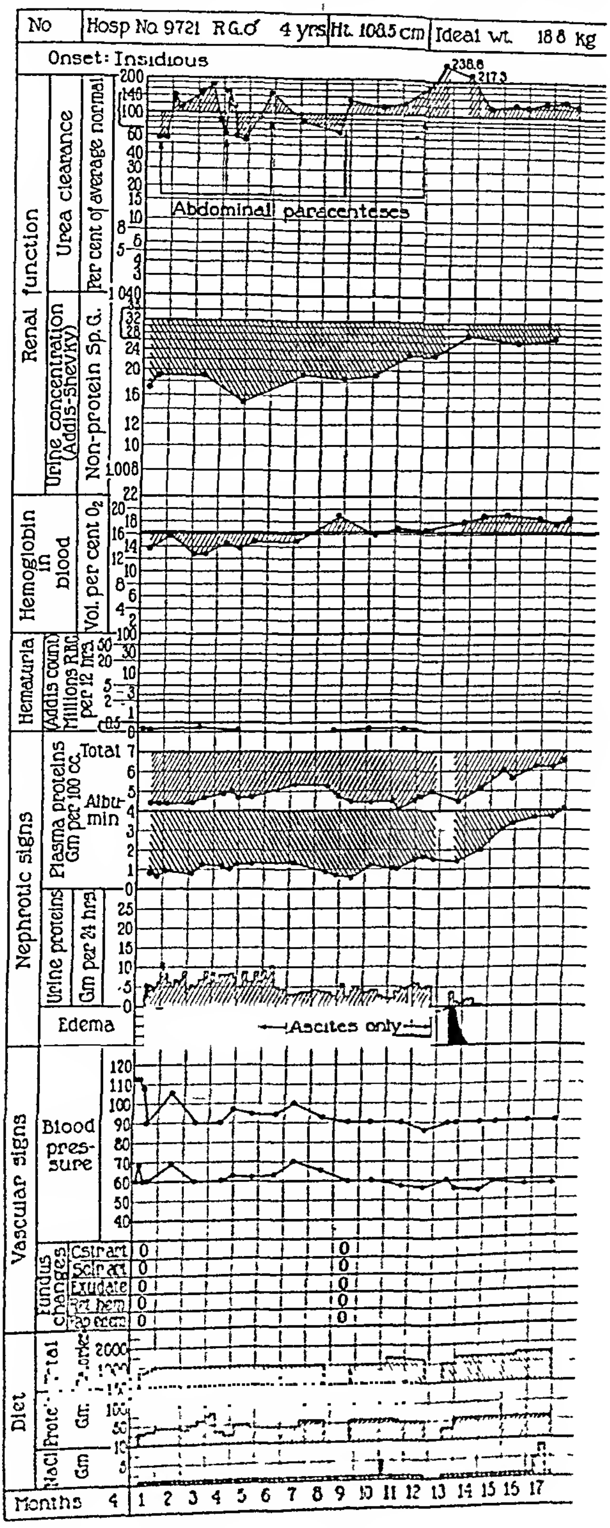

No
Hosp No. 9721 R.G.♂ 4 yrs
Ht. 108.5 cm
Ideal wt. 18.8 kg
Onset: Insidious
Renal function
Urea clearance
Per cent of average normal
238.8
217.3
Abdominal paracenteses
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
1.040
1.008
Hemoglobin in blood
Vol. per cent O₂
Hematuria
Addis count Millions RBC per 12 hrs.
Nephrotic signs
Plasma proteins Gm per 100 cc.
Total
Albumin
Urine proteins
Gm per 24 hrs.
Edema
Ascites only
Vascular signs
Blood pressure
Fundus changes
Cs ir art
Scl r art
Exudate
Ret hem
Edema
Diet
Total calories
Protein
Gm.
NaCl
Gm
Months
4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

CHART 1

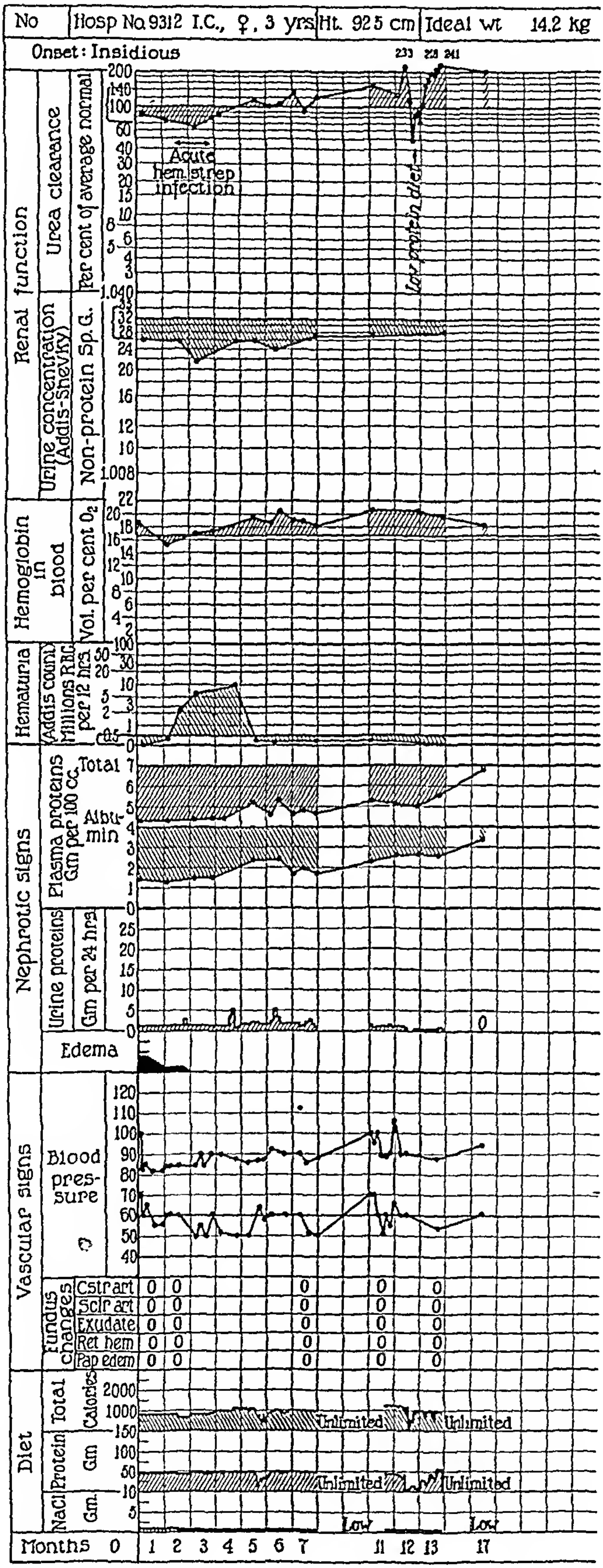

No
Hosp No. 9312 I.C., ♀, 3 yrs
Ht. 92.5 cm
Ideal wt 14.2 kg
Onset: Insidious
Renal function
Urea clearance
Per cent of average normal
233
231
241
200
140
100
60
40
30
20
15
10
8
6
5
4
3
Acute hem. strep infection
low protein diet
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
1.040
32
28
24
20
16
12
10
1.008
Hemoglobin in blood
Vol. per cent O2
22
20
18
16
14
12
10
8
6
4
2
Hematuria
Addis count Millions RBC per 12 hrs.
100
50
30
20
10
5
3
2
1
0.5
0
Nephrotic signs
Plasma proteins Gm per 100 cc.
Total
Albumin
7
6
5
4
3
2
1
0
Urine proteins
Gm per 24 hrs.
25
20
15
10
5
0
Edema
Vascular signs
Blood pressure
120
110
100
90
80
70
60
50
40
Fundus changes
Cstr art
Sclr art
Exudate
Ret hem
Pap edem
Diet
Total
Calories
2000
1000
150
Protein
Gm
100
50
10
NaCl
Gm.
5
Unlimited
Unlimited
Unlimited
Unlimited
Low
Low
Months
0
1
2
3
4
5
6
7
11
12
13
17

CHART 2

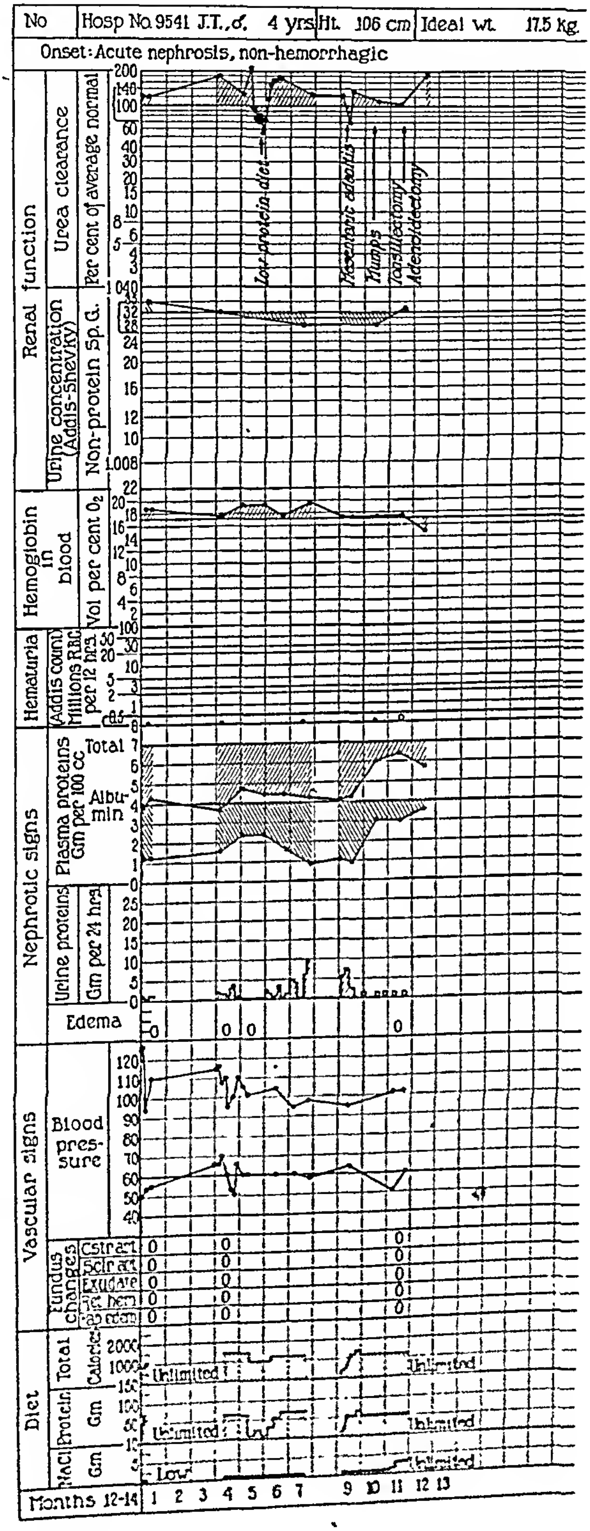

No
Hosp No. 9541 J.T., ♂. 4 yrs
Ht. 106 cm
Ideal wt. 17.5 Kg.
Onset: Acute nephrosis, non-hemorrhagic
Renal function
Urea clearance
Per cent of average normal
200
140
100
60
40
30
20
15
10
8
6
5
4
3
Low protein diet
Mesenteric adenitis
Mumps
Tonsillectomy
Adenoidectomy
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
1.040
36
32
28
24
20
16
12
10
1.008
Hemoglobin in blood
Vol per cent O₂
22
20
18
16
14
12
10
8
6
4
2
Hematuria
Addis count Millions RBC per 12 hrs.
100
30
20
10
5
3
2
1
0.5
Nephrotic signs
Plasma proteins Gm per 100 cc
Total
Albumin
8
7
6
5
4
3
2
1
0
Urine proteins
Gm per 24 hrs
25
20
15
10
5
0
Edema
0
Vascular signs
Blood pressure
120
110
100
90
80
70
60
50
40
Fundus changes
Cstract
Sclract
Exudate
Ret hem
Pap edem
Diet
Total Calories
2000
1000
Unlimited
Protein Gm
150
100
50
NaCl Gm
15
5
Low
Months 12-14
1
2
3
4
5
6
7
9
10
11
12
13

CHART 3

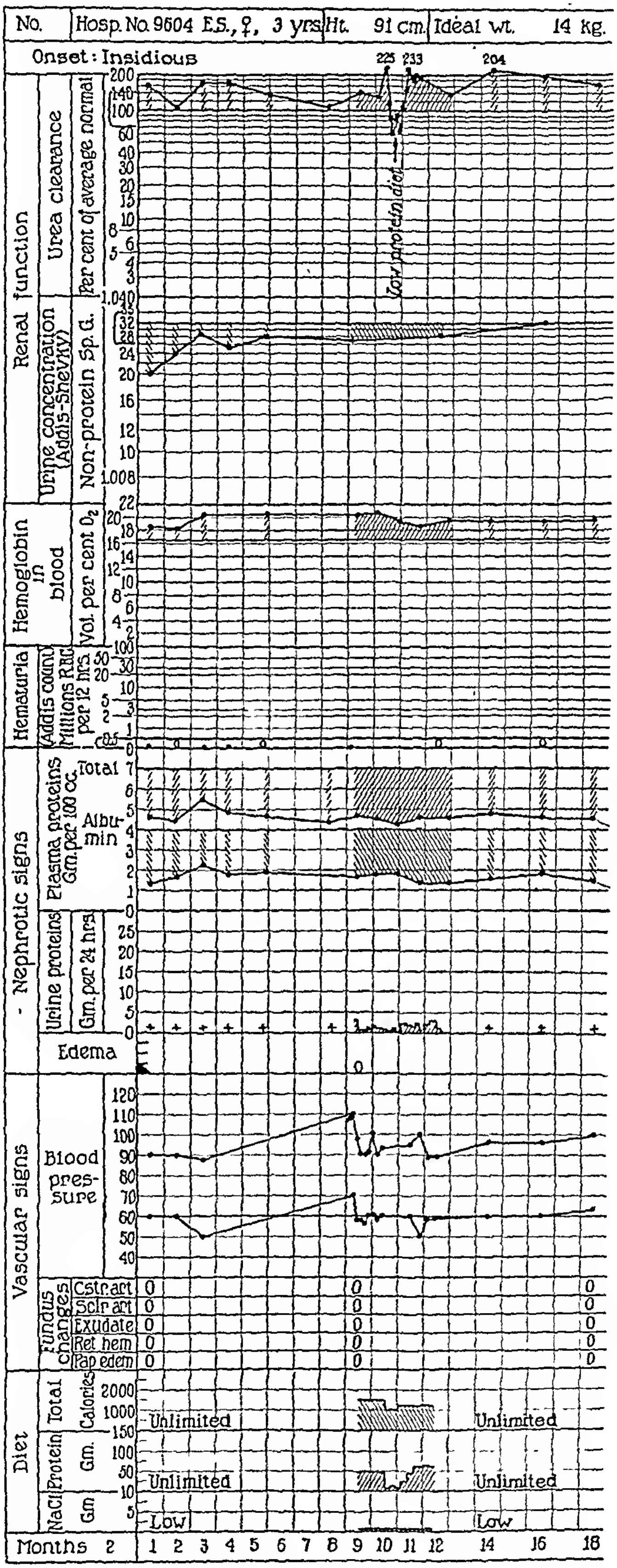

No.
Hosp. No. 9604 E.S., ♀, 3 yrs
Ht. 91 cm.
Ideal wt. 14 kg.
Onset: Insidious
225
233
204
Renal function
Urea clearance
Per cent of average normal
200
140
100
60
40
30
20
15
10
8
6
5
4
3
Low protein diet
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
1.040
32
28
24
20
16
12
10
1.008
Hemoglobin in blood
Vol. per cent O₂
22
20
18
16
14
12
10
8
6
4
2
Hematuria
Addis count Millions RBC per 12 hrs.
100
50
30
20
10
5
3
2
1
0.5
0
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
7
6
5
4
3
2
1
0
Urine proteins Gm. per 24 hrs.
25
20
15
10
5
0
Edema
Vascular signs
Blood pressure
120
110
100
90
80
70
60
50
40
Fundus changes
Cstr. art
Sclr. art
Exudate
Ret. hem
Pap. edem
Diet
Total Calories
2000
1000
Unlimited
Protein Gm.
150
100
50
10
Unlimited
NaCl Gm.
5
Low
Months 2
1 2 3 4 5 6 7 8 9 10 11 12 14 16 18

CHART 4

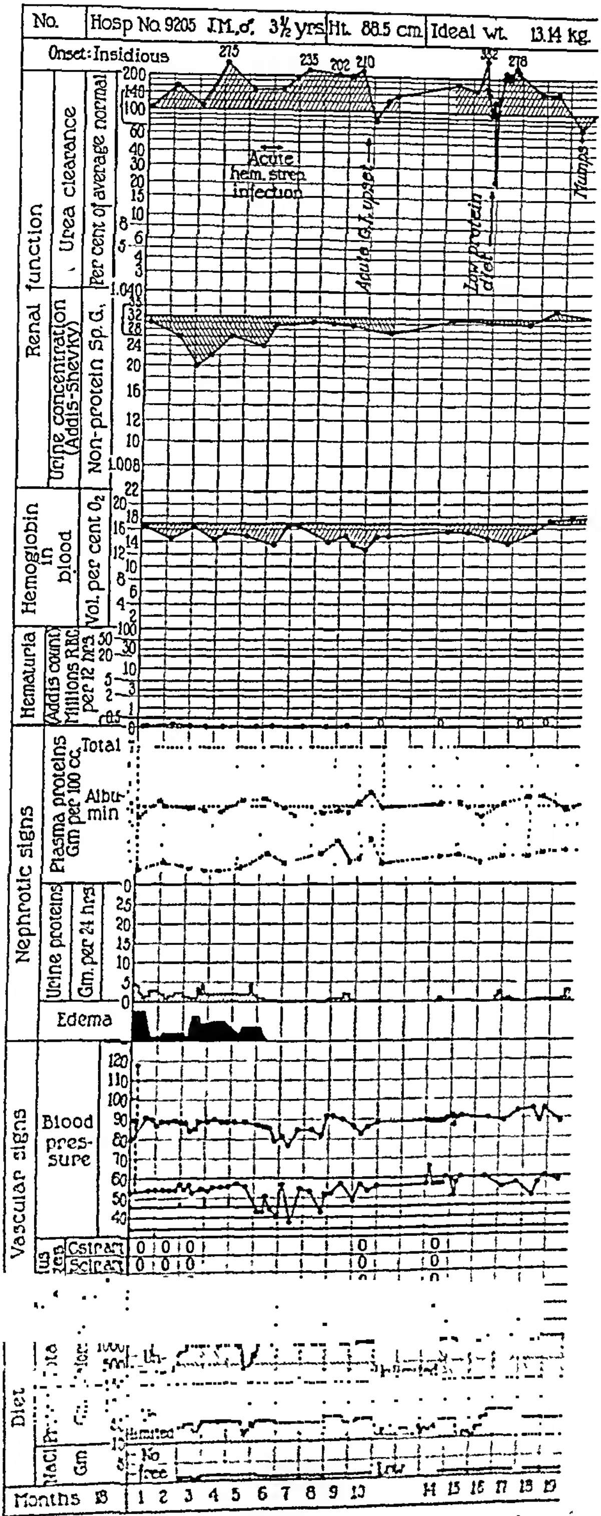


CHART 5

CHARTS 1 TO 5 (inclusive).—Graphic representation of course of patients, and nature and degree of renal disturbance.

No attempt was made to keep the fat in the diet at a very low level, as it is an impression gained in a previous study[9] that the children take the high-protein diets more readily when an adequate amount of fat is fed; this is probably because without fat restriction a more varied and palatable diet can be given. The difficulty in getting the children to eat the low-protein diet was not due to the relative increase in fat calories, as previously some of these children were fed a diet containing up to 4.25 gm. of fat per kilo. of ideal body weight and these diets were taken as long as 2 months without difficulty.[9] At another time an attempt was made to carry out observations on these children on a meat- and fish-free diet. Difficulty was encountered in getting them to take an adequate caloric diet on this régime even a week. The administration of 5 gm. of fresh brewer's yeast daily is thought to have been of considerable value in maintaining a zest for food.

In calculating the average daily balance on each diet, the first 3 or 4 days of each period on that diet are omitted, in order to eliminate significant effects of the preceding period. Daily estimations of non-protein urine nitrogen were done and the balance periods were begun after equilibrium had apparently been reached on each diet.

The urinary protein is omitted from the balance because it represents nitrogen which has been assimilated, and its loss might be described as mechanical rather than anabolic. The differences between nitrogen intake and excreted non-protein nitrogen seem to indicate assimilated nitrogen more accurately than would the difference between intake and total nitrogen excretion when the latter includes urinary protein losses.

Analyses. The non-protein urinary nitrogen output was determined in urine deproteinized with trichloroacetic acid. The nitrogen in the protein-free filtrate was determined gasometrically by the micro-Kjeldahl method of Van Slyke.[14] The nitrogen intake was calculated from dietary tables used in the hospital which have been compiled from standard works on food values.[1,5,8,12] Control nitrogen analyses of diets have shown good agreement with the values calculated from the tables. Blood-urea nitrogen values were obtained by the gasometric method of Van Slyke and Kugel.[15] Urine protein estimations were made by the method of Shevky and Stafford.[13] Fecal nitrogen was not measured. Its omission from the balance is not believed to affect the validity of the conclusions, since the fecal nitrogen is reported to approximate with relative constancy about 10% of the nitrogen intake, in the absence of diarrhea or a diet which is unusually rich in roughage substance.[11,17] These diets were designed to avoid either diarrhea or marked fluctuations in roughage content.

Results. The children seemed to be normally active on all the diets offered except the very low-protein diet. When this diet was fed for a week, a definite loss of activity and interest in their

TABLE 1.—NITROGEN METABOLISM ON THE VARIOUS DIETS FED.

Patient.	Duration of balance period, days.	Weight.		Average daily food intake.									Average daily metabolized nitrogen output.				Assimilated retained nitrogen daily average, gm.	Blood urea nitrogen per 100 cc., mg.
							Calories derived from:							Nitrogen balance.				
		Actual, kg.	Ideal, kg.	Protein, gm.	Carbohydrate, gm.	Fat, gm.	Protein, %.	Carbohydrate, %.	Fat, %.	Total calories.	Protein per kilo ideal body weight, gm.	Total nitrogen fed, gm.	Total non-protein urine nitrogen, gm.	Gm.	Corrected for fecal nitrogen, gm.	Proteinuria, gm.		
J. M.	10	17.0	15.0	50	137	49	17.0	47.0	36.0	1200	3.3	8.000	6.313	1.687	0.887	0.44	0.815	8.11
	5	17.5	..	9	126	51	3.6	50.4	46.0	1000	0.6	1.440	1.181	0.259	0.115	0.20	0.083	3.53
	3	17.9	..	18	153	35	7.0	61.5	31.5	1000	1.2	2.880	1.221	1.659	1.371	0.10	1.355	3.40
	3	17.2	..	36	126	39	14.4	50.6	35.0	1000	2.4	5.760	2.607	3.093	2.517	0.16	2.492	3.80
	3	16.1	..	54	108	39	22.0	43.0	35.0	1000	3.6	8.640	5.083	3.557	2.093	0.34	2.039	9.08
	3	17.0	..	72	123	47	24.0	41.0	35.0	1200	4.8	11.500	9.600	1.900	0.850	1.07	0.690	10.17
R. S.	10	16.3	15.0	50	149	78	13.0	40.0	47.0	1500	3.3	8.000	5.453	2.547	1.747	2.47	1.352	9.05
	5	16.2	..	9	126	51	3.6	50.4	46.0	1000	0.6	1.440	1.144	0.290	0.152	0.54	0.066	3.91
	3	16.3	..	16	156	35	6.4	62.4	31.5	1000	1.0	2.560	1.435	1.125	0.869	0.92	0.722	4.27
	3	16.0	..	32	162	47	10.3	54.7	35.0	1200	2.1	5.120	2.333	2.787	2.275	2.70	1.842	4.00
	3	16.0	..	48	116	47	16.0	49.0	35.0	1200	3.2	7.680	3.473	3.207	2.439	2.00	2.119	7.84
	3	16.3	..	64	131	47	21.0	41.0	35.0	1200	4.2	10.250	7.530	2.720	1.695	2.00	1.375	10.68
J. T.	10	18.4	17.5	53	118	78	15.0	38.0	47.0	1500	3.0	8.490	6.408	2.082	1.233	0.60	1.137	6.87
	5	18.1	..	9	126	51	3.6	50.4	46.0	1000	0.5	1.440	1.295	0.145	0.001	0.20	−0.031	4.62
	3	18.2	..	18	153	35	7.0	61.5	31.5	1000	1.0	2.880	2.269	0.611	0.323	0.41	0.257	0.04
	3	18.1	..	36	159	47	12.0	53.0	35.0	1200	2.0	5.760	3.889	1.871	1.295	2.05	0.967	6.95
	3	18.2	.	54	191	47	18.0	47.0	35.0	1200	3.1	8.650	5.860	2.790	1.925	0.70	1.813	8.79
	3	18.2	.	72	123	47	24.0	41.0	35.0	1200	4.1	11.500	9.653	1.847	0.697	1.72	0.422	11.40
I. C.	5	11.6	13.6	10	145	51	11.0	18.0	38.0	1200	2.9	6.400	4.575	1.825	1.185	1.62	0.925	6.47
	5	11.3	..	8	98	48	4.0	44.0	52.0	860	0.6	1.312	0.939	0.373	0.242	0.30	0.194	3.34
	3	11.2	..	14	156	35	5.6	62.9	31.5	1000	1.0	2.240	1.584	0.656	0.432	0.36	0.374	3.63
	2	11.2		28	134	39	11.2	53.8	35.0	1000	2.1	4.480	2.153	2.327	1.879	0.80	1.751	3.66
	2	11.2	..	12	121	39	17.0	48.0	35.0	1000	3.1	6.720	3.710	3.010	2.338	0.84	2.204	6.70
	3	11.2	..	56	108	39	22.0	13.0	35.0	1000	4.1	8.962	6.245	2.717	1.821	0.95	1.669	8.18
R. G.	1	25.6	18.0	10	123	39	16.0	49.0	35.0	1000	2.2	6.400	4.039	2.361	1.721	5.31	0.871	9.75
	5	26.0	..	50	113	39	20.0	45.0	35.0	1000	2.8	8.000	5.152	2.848	2.048	6.28	1.013	12.48
	3	26.3	.	60	102	39	24.0	41.0	35.0	1000	3.3	9.600	6.323	3.277	2.317	7.18	1.170	16.56
	3	27.2	.	70	92	39	28.0	37.0	35.0	1000	3.9	11.200	8.055	3.145	2.025	6.86	1.030	20.73
	3	21.0	..	80	82	39	32.0	33.0	35.0	1000	4.4	12.800	10.790	2.010	0.730	7.35	−0.445	27.06
	4	22.1	.	30	132	39	12.0	53.0	35.0	1000	1.7	4.800	2.504	2.296	1.816	6.16	0.830	13.44
	4	22.0	..	20	142	39	8.0	57.0	35.0	1000	1.1	3.200	2.099	1.101	0.781	6.07	−0.191	6.31

surroundings could be noted. At the same time it became more difficult to get the children to eat. For this reason the very low-protein diet was fed for 2 short periods separated by a period of slightly greater protein intake. The high-protein diets were well taken by all the children and there seemed to be no evidence of any approach to a saturation level of the appetite for protein foods.

Nitrogen Assimilation. The results are summarized in some detail in Table 1 and Charts 6 and 7. The charts show comparisons of total nitrogen intake with non-protein urinary nitrogen output. The nitrogen of the urine protein is not included in the output because it represents not only a metabolized fraction but also an assimilated portion of the diet, which is lost only through the accident of filtration and has no evident bearing on ability to use dietary protein. Balances are, however, calculated subtracting this loss to obtain information regarding tissue nutrition (Table 1). The 4 children whose protein intake varied from 0.5 to 4 gm. per kilo. showed, as would be expected, wide fluctuations in the excretion of nitrogen in the urine. On the very low-protein diets all the children were able to maintain themselves in a slight positive balance when proteinuria is excluded from consideration. When 1, 2 and 3 gm. of protein per kilo. were fed, increasing amounts of nitrogen were retained. When, however, more than 3 gm. were fed, excretion of urinary non-protein nitrogen increased to such an extent

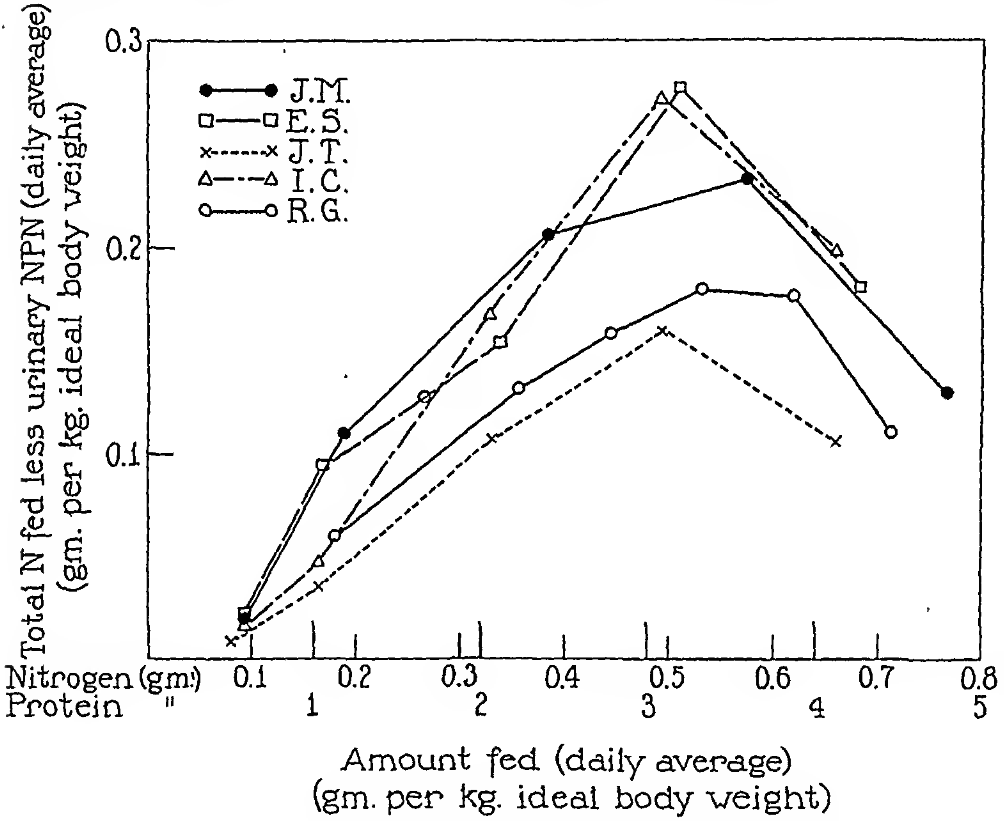
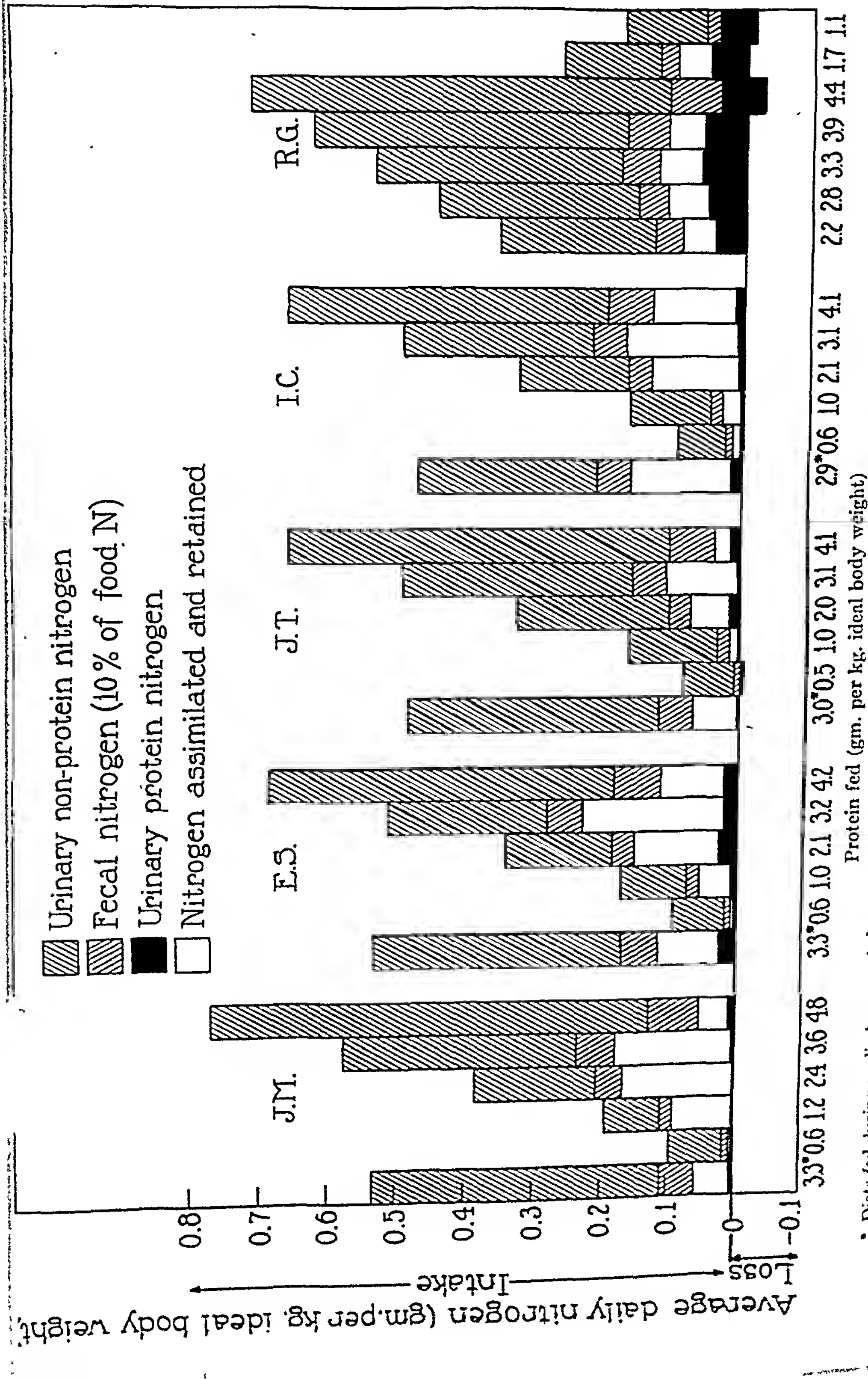


CHART 6.—The relation of nitrogen excretion in the urine to varying nitrogen intakes.



* Diets fed during preliminary period

CHART 7.—Nitrogen assimilated on varying nitrogen intakes on the highest diet that the increment of urine non-protein nitrogen alone was greater than the increment of intake. Consequently the assimilation of nitrogen was less on the very high diet than on the more moderate intake. This observation remained constant, regardless of the order in which the diets were fed. R. G. showed a marked increase in nitrogen storage when the protein in the diet was reduced from 4.4 gm. per kilo. to 1.7 gm. The results indicate that optimum nitrogen assimilation occurred when the diet contained about 3 gm. of protein per kilo., and that increasing the protein intake beyond this optimum actually diminished nitrogen retention. The extent of this diminution is apparent when one examines the balance for nitrogen assimilated and retained on the highest protein diet. On this diet R. G. was in fact on a negative nitrogen balance, indicating tissue wastage. Maximum nitrogen assimilation was obtained with protein intakes at 3.1, 3.1, 3.2, 3.3 and 3.6 gm. per kilo. of ideal body weight in the 5 respective patients. In each of 4 patients there was a smaller retention of nitrogen on the diet with 3 gm. of protein during the preliminary period when the fat content was greater. The carbohydrate content of these diets was in each case slightly greater than during the second period when a lesser quantity of fat was fed. The fifth patient (R. G.) was not placed during any period on the very low-protein intake. However, when his protein intake exceeded 3.3 gm. per kilo. of ideal body weight he showed the same phenomenon retaining less nitrogen than on an intake of 2 to 3 gm.

In Chart 7 are summarized, as measures of nitrogen assimilation, the balances calculated by subtracting the urinary non-protein nitrogen from the food nitrogen. Slight changes in caloric intake appeared to exert no effect on nitrogen retention. This observation was made for adults by Keutmann and Bassett.[7]

Proteinuria. In the first 4 patients proteinuria rose and fell with protein intake. In the fifth patient, however, the loss of protein in the urine was extraordinarily constant regardless of the protein intake. The proteinuria shown by these patients was quite constant from day to day on constant food intake and could be estimated with sufficient accuracy by determinations made on 2 or 3 days of each week.

Blood Urea. High-protein diets increased the blood urea nitrogen values only slightly above the level maintained on average diet. We have previously shown[4] that nephrotic children increase their urea clearances when the protein intake is raised. This increased renal activity prevents the blood urea rise that would otherwise occur. On the other hand, the very low-protein diets did affect the blood urea, which showed a sharp reduction to very low levels. The children with a more pronounced glomerular element do show an increase in blood nitrogen on high diets and lesser increases in urea clearance.

Water Excretion. On the total urine volume, the total fluid intake, or the ratio of fluid intake to urine volume, the different diets had no marked effect.

Discussion. When the optimum level of protein intake for retention observed in our patients is compared with the optimum for normal children, the surprising fact becomes apparent that there are no marked differences between the two groups. Thus, Holt and Fales,[6] in a study of the protein requirements of children found that the protein intake optimal for growth and condition varied from 4 gm. per kilo. at 1 year to 2.6 gm. at 6 years. Wang, Hawks and Hays,[16] in a study of the metabolism of undernourished children, including nitrogen balances, came to the conclusion that malnutrition *per se* makes no difference in the ability of the child to assimilate nitrogen, that in fact undernourished and malnourished children actually retained nitrogen better than normal children. In a subsequent study Wang, Hawks and Kaucher[17] recommended a protein intake of 4 gm. per kilo. for undernourished children but they made no studies comparing the relative efficiency of nitrogen retention at 4 gm. per kilo. as compared with an intake at a 3 gm. per kilo. level. Daniels, Hutton, Knott, Wright, Everson and Scoular,[2] from a study of the protein needs of pre-school children, came to the conclusion that children of this age should receive approximately 3.2 gm. of protein per kilo. of ideal body weight. Thus it is apparent that studies of other authors on the protein requirements of normal children have yielded results showing optimal growth and general condition with about the same protein intakes which yielded maximal nitrogen retention in our nephrotic children. Some of the results suggest that addition of fat beyond a certain amount decreases nitrogen retention. The experiments were not planned to bear on this point, and the results are not decisive, but they appear to be sufficiently suggestive to merit passing attention.

Our results offer no support for the thesis that in patients with albuminuria the optimal protein intake can be calculated by adding to the ordinary maintenance diet an amount of protein equal to or proportional to the protein loss in the urine.

The total failure to assimilate protein fed above 3.3 gm. per kilo. serves to emphasize the point that physiologically optimum intake of a given food is not necessarily the greatest amount that can be handled by the alimentary tract. Still less do our results justify forcing high-protein diets, as by addition of casein or lactalbumin, to the point of gastro-intestinal rebellion.

On the other hand, our results obtained with children do not disprove for adults the usefulness of the rule of Peters and Bulger,[10] whereby the protein fed is 75 gm. plus the amount of protein lost in the urine; the amounts thus calculated are seldom above 1 to 1.5 gm. per kilo., and may never exceed the usual assimilating optimum of adults. Keutmann and Bassett[7] found in their studies in adults that, over the ranges of protein intake studied, with beef-serum proteins as the dietary constituent this phenomenon of decreasing utilization was noted, while with other proteins it was not apparent. These studies are not exactly comparable to the work reported here, since the only comparison available is over a much smaller range of protein intake, and the studies were of fractional rather than total assimilation.

Summary and Conclusions. Five children of 5 years have been observed continuously over a period of 54 days in nitrogen balance studies with diets which varied in protein content from 0.5 to 4 gm. per kilo. of ideal body weight.

Maximum nitrogen retention occurred in 4 patients when the dietary protein intake was about 3.2 gm. per kilo. of ideal body weight, and in the fifth patient when the intake was 3.6 gm. per kilo. Feeding more protein resulted in actually less retention.

The protein intakes producing maximal assimilation in our nephrotic children were similar to those found by other observers to be optimal for growth and general condition in normal children. Our data do not indicate that in the nephrotic syndrome the loss of protein in the urine is accompanied by compensatory increase in ability to assimilate food protein.

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CLINICAL OBSERVATIONS ON THE EFFECTS OF CHOLINE COMPOUNDS IN NEUROLOGIC DISORDERS, WITH SPECIAL REFERENCE TO MÉNIÈRE'S SYNDROME.*

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The physiologic and pharmacologic properties of compounds of choline have been extensively investigated in recent years. For discussions of the actions of these drugs and their clinical applications the reader is referred to a few of the many valuable contributions in the literature.[1–5, 7–9] The vasodilating effects of these substances on the vessels supplying the viscera in mammals,[2] and the relief of vertigo in one patient as reported by Starr[8] suggested that choline compounds might be of value in the treatment of Ménière's syndrome, and possibly in the treatment of other disorders of the central nervous system in which vascular spasm might conceivably play a part. At the suggestion of Starr, a clinical investigation of the effects of such compounds was begun in the Neurologic Department of the Hospital of the University of Pennsylvania in 1933. The work was intended primarily to include only cases of Ménière's syndrome, but as opportunity arose during the course of the investigation observations were made on certain other types of cases.

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* The studies reported herein were made principally in the Neurological Wards and Outpatient Department of the Hospital of the University of Pennsylvania, Philadelphia, in the service of Dr. William G. Spiller, as a part of the work of the D. J. McCarthy Foundation of the University of Pennsylvania.

Ménière's Syndrome. In this report the term Ménière's syndrome is used to designate combinations of such symptoms as vertigo, nausea, tinnitus aurium and progressive deafness, occurring usually in middle-aged or elderly persons without relevant local or systemic disease other than chronic degenerative changes, particularly of arteriosclerotic character. Although early descriptions of the syndrome attributed the symptoms to hemorrhage into the labyrinthine structures, it is now recognized that chronic degenerative processes affecting those structures, and arteriosclerotic changes in the vessels supplying them and possibly also of the vessels supplying the central pathways may produce the clinical picture without actual demonstrable hemorrhage. Spasm of the vessels supplying the labyrinth is now thought to be the cause in many cases.[6]

Six patients presenting Ménière's syndrome were classified after thorough clinical and laboratory investigation as cases of the arteriosclerotic or vasospastic type. These patients were treated by the oral administration of either acetyl beta methylcholine chloride or ethyl beta methylcholine chloride.* A résumé of the relevant data in these cases together with the results of treatment is given in Table 1. These 6 patients were observed in a total of 14 severe exacerbations and 2 minor ones. The approximate degree of relief of the several symptoms as indicated in terms of percentages represents in each case the degree of relief of the subjective symptoms as estimated by the patient, and the objective changes as estimated by the examiner after observation. It is not implied that the figures represent an accurate objective standard of measurement. Of these exacerbations observed, 11 major flare-ups occurred during periods in which the patient was taking no choline in any form, one major exacerbation occurred during a period in which the patient was taking the average normal therapeutic dose regularly, and 2 occurred during periods in which the patient was taking less than the average

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* The drugs used were kindly furnished by Merck & Co., Rahway, N. J.

TABLE 1.—SUMMARY OF CASE DATA.

Case No.	1	2	3	4	5	6
Age (yrs.).	56	54	42	52	58	29
Sex.	M.	F.	M.	M.	M.	M.
Total duration of symptoms	10 yrs.	17 mos.	2 yrs.	3 weeks	2 yrs.	11 mos.
Duration of immediate exacerbation at time choline treatment was started	2 yrs.	17 mos.	1 yr.	3 weeks	4 mos.	11 mos.
Duration of choline treatment when first distinct relief was noted	Less than 1 wk.	Less than 1 wk.	2 days	5 days	17 days	?
Duration of choline treatment at time maximum degree of relief was obtained (wks.)	1	3	4	4	17	2
Approximate degree of relief:						
Vertigo	Variable 90–100%	Variable 90–100%	75%	75%	75%	10%
Headache	Variable 75–100%	90%	40% (?)	90%	100%	Never present
Nausea	100%	100%	Never present	Vomited only at onset	Never present	Never present
Ataxia	100%	100%	90%	90%	80%	20%
Deafness	0	0	Not known	Not known	Not known	Not known
Tinnitus	Variable 0–50%	0	0	Never present	0	Not known

In Case 3, headache was relieved 50% by abstinence from tobacco before choline therapy was started and was 90% relieved 1 month after starting choline therapy. In Case 4, occupational exposure to paint solvent and denatured alcohol fumes; resumed same occupation 5 weeks after choline therapy had been instituted and had no return of symptoms. Case 6 had possible occupational connection in form of middle-ear trauma as result of playing wind instrument in orchestra.

therapeutic dose. One of the minor exacerbations occurred while the patient was taking the average normal therapeutic dose, and one minor attack occurred during a period in which less than the therapeutic dose was being used.

The usual effective therapeutic and prophylactic oral dose of acetyl beta methylcholine chloride was found to be 0.08 gm. 3 times daily. The average dose of ethyl beta methylcholine chloride was 0.006 to 0.008 gm. 3 times daily. The drugs were prescribed in dilute aqueous solution for convenience in measuring and varying the dosage, and so that as a control, distilled water could be substituted at will for the practically tasteless, odorless and colorless choline solutions. Larger individual or total daily dosages were found to cause toxic manifestations of mild form in most instances, while doses substantially lower were found to be less dependable in the prevention of, or the relief of the attacks.

In general, of the 6 patients included in this series, 5 obtained satisfactory relief from the disabling features, namely the vertigo, headache, ataxia and nausea, when present, on the choline therapy. In these 5 patients the continued use of choline during intervals of quiescence usually but not invariably appeared to prevent the recurrence of exacerbations or to minimize their severity, while discontinuance of its prophylactic use frequently was followed by recurrence of symptoms. The sixth patient obtained only slight relief of the vertigo and the ataxia, which were his only pronounced symptoms. The effect of choline on the impairment of hearing and on the tinnitus was negligible in each instance.

Severe toxic symptoms were encountered only on one occasion in one patient, this occasion having resulted from a misunderstanding by the patient of the instructions given her as a result of which she took the drug indiscriminately in large doses. When they occurred, the milder subjective toxic manifestations usually noted by the patient consisted of a feeling of giddiness and faintness, almost always accompanied by a sense of "emptiness" in the abdomen or in the head or both, in addition to the well recognized symptoms of increase in salivary secretion, increase in the secretions of sweat and of tears; and diarrhea, and nausea. The patients were able to differentiate the giddiness or emptiness of choline toxicity from the vertigo and faintness of Ménière's syndrome. A sense of constriction in the chest or an objective flushing of the skin of the face and neck was seldom encountered. No cumulative effect was noted in any case, the longest period of uninterrupted use of average therapeutic doses being 5 months. On the other hand, there apparently was no tolerance developed after prolonged administration of the drug.

Three additional cases not included in the above series were diagnosed clinically as Ménière's syndrome and were treated with choline compounds with apparently favorable effect. These cases were not included in the series, however, because of the impossibility of complete clinical and laboratory studies, or because of other possible etiologic factors which might have confused the picture. One of these patients had pronounced symptoms of several years' duration and his symptoms were markedly reduced within a few days after the institution of choline therapy. However, several weeks later during the course of other medical investigations it was found that he was allergic to certain foods and the elimination of the allergens was reported subsequently to have prevented further attacks after the use of choline had been discontinued. The other 2 patients, although apparently relieved by choline were not seen a sufficient number of times nor studied in sufficient detail to warrant inclusion in the series.

Major Trigeminal Neuralgia. One patient who had major trigeminal neuralgia affecting the third division on the right side was treated by orally administered choline preparations. Since the time of the onset nearly 3 years prior to the period of observation there had been two remissions of 3 to 4 months' duration each and a few other periods of 1 or 2 weeks of partial relief. During the 3 months before choline therapy was started there had been very slight and very gradual diminution in the severity of the pains. Ethyl beta methyl choline chloride orally in doses of 0.0166 gm. 3 times daily was prescribed. In the first 6 days there was rapid improvement, and 11 days after the beginning of treatment the sharp shooting pains had entirely disappeared and only a residual sensation of soreness of the gums on the affected side remained. This also entirely subsided in about 3 months. The dosage of the choline preparation was reduced to the maintenance level of 0.005 gm. to 0.008 gm. after the first 3 weeks and the drug was discontinued altogether after 5 months. Three months after discontinuing choline there was recurrence of very mild pain, but the discomfort was so slight that no treatment was required.

This patient also had a persistent motor tic of 12 years' duration affecting the left corner of the mouth. This motor tic began to subside a little less than 2 months after the institution of choline therapy and it had disappeared almost completely at the end of 6 months.

Intermittent Claudication. One patient with marked peripheral arteriosclerosis and intermittent claudication obtained a considerable degree of relief while taking choline preparations. Following his customary route in walking to the clinic he found that under such therapy he could walk twice as far at his usual rate of speed before the pains forced him to rest.

Miscellaneous Observations. Although in the following types of conditions no encouraging therapeutic responses were noted, and no detailed studies were made, nevertheless definite clinical impressions of the negative value or of the actually undesirable effects of choline administration were gained and should be recorded. The rigidity associated with basal ganglia lesions and the spasticity of upper motor neuron lesions appeared to increase under choline therapy, whereas motor power was unaffected. Spontaneous pain associated with thalamic lesions was unaffected. Acquired myotonia secondary to alcoholic peripheral neuritis was not distinctly influenced by the use of choline orally or by inotophoresis of the affected parts. Migraine, presumably of the allergic type, was not relieved, nor did choline derivatives have any distinct effect upon the frequency or severity of epileptic seizures. Prolonged administration in one case of malignant hypertension did not materially influence the blood pressure level or the course of the disease. Nausea, vertigo, tinnitus or hearing defect occurring not as Ménière's syndrome but associated with acute or chronic infections of the upper respiratory tract, the ears, or the mastoids, or as symptoms secondary to organic involvement of the central nervous system such as multiple sclerosis or vascular thrombosis were not relieved by choline therapy.

Summary and Conclusions. Clinical observations of the effects of certain choline derivatives have been made in a number of neurologic conditions. Of 6 cases presenting Ménière's syndrome 5 were distinctly relieved in the majority of acute exacerbations by the oral use of acetyl beta methylcholine chloride or of ethyl beta methylcholine chloride, and the acute exacerbations were apparently less frequent and less severe when these drugs were taken prophylactically. One patient having major trigeminal neuralgia and one having intermittent claudication apparently were relieved by these choline compounds taken orally. Negative or unfavorable effects of choline in a miscellaneous group of conditions are reported.

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HUMAN AUTONOMIC PHARMACOLOGY.

VII. THE EFFECT ON THE NORMAL CARDIOVASCULAR SYSTEM OF ACETYL–BETA–METHYLCHOLINE CHLORIDE, ATROPINE, PROSTIGMIN, BENZEDRINE—WITH ESPECIAL REFERENCE TO THE ELECTROCARDIOGRAM.*

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IN previous communications,[16–19b] we have reported upon the effects of certain drugs which act primarily upon the autonomic nervous system. The drugs selected for study have been acetyl-beta-methylcholine chloride (mecholyl), benzedrine sulphate, atropine, and prostigmin, a drug related to physostigmin. Certain effects upon the cardiovascular system having been noted, it was felt that a systematic study of the effects of these various drugs upon the heart and particularly upon the electrocardiogram might throw further light on the actions of the autonomic nervous system in general and on the sites of autonomic activity in the heart in particular.

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* Aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

Previous studies of the effects of these drugs upon the heart have been for the most part made upon animals, although a few, notably those by Starr and his co-workers[23a,b,24] and by Nahum and Hoff,[20] have dealt with human subjects. Starr's papers have been chiefly concerned with the use of mecholyl in the arrhythmias, especially paroxysmal auricular tachycardia while the papers of Nahum and Hoff have dealt with abnormal states such as hyperthyroidism. Carmichael and Fraser[3] studied the effects of giving large doses of acetylcholine intravenously to a few normal subjects; they were able to enhance these effects considerably by the previous administration of physostigmin. Page[21] studied the effects of mecholyl on the heart of hypertensive patients, using the electrocardiogram. The present paper is concerned with a study of the effects on the circulation, more specifically upon the electrocardiogram, of the various drugs mentioned above, given either singly of in various combinations. The data obtained, aside from their objectivity and predictability, have been valuable both theoretically as in understanding the mechanisms of acetylcholine action and practically, in appreciation of certain clinical conditions such as heart block.

Methods and Material. Male patients with dementia præcox were used. Numerous examinations and laboratory tests over a period of years, as described in previous papers, had shown them to be physiologically normal despite their obvious mental disorder. The patients selected were in addition quite coöperative. Patients with hypertension or with evidences of arteriosclerosis or vasomotor conditions were excluded. All tests were conducted in the basal postabsorptive state conditions. After a rest period of about one-half hour in the laboratory the experiment was begun.

The drugs* used were as follows: (1) Mecholyl, always given subcutaneously dissolved in distilled water; the usual dosage was 25 mg., but this was varied from time to time according to the conditions of the experiment; (2) atropine sulphate, which was given either intramuscularly or intravenously usually in doses of gr. 1/50 (1.3 mg.); (3) prostigmin given subcusubcutaneously in dosage of 0.5 to 1.5 mg.; (4) benzedrine sulphate given subcutaneously or intramuscularly in dosage of 30 to 40 mg.

All experiments were conducted with the patient lying down. Blood pressure readings and electrocardiographic tracings were taken frequently and the latter were in some cases taken uninterruptedly throughout the experiment. Because of the rapidly changing events in the cardiac cycle, particularly when mecholyl was used, tracings with only one lead (Lead II) were usually made. In the electrocardiograms, careful analyses were made of the cardiac rate, the rhythm, the shape and voltage of the various waves, the length of the *P–R* interval, and the ratio of the *P–R* interval to the time of the complete cardiac cycle.

Results. 1. *Mecholyl.* The clinical effects which follow the subcutaneous administration of 10 to 25 mg. of mecholyl have already been noted by us.[18,19a] These begin within 30 seconds after the drug is given and consist of marked flushing of the face and chest, lacrimation, salivation, rhinorrhea, and extreme perspiration. Within 30 to 90 seconds the blood pressure falls abruptly and the pulse rate rises. Though the reaction varies, most subjects will obtain a maximum effect with 25 mg., although some require only 10 mg. and others 40 mg. Mecholyl was given as the first drug in 16 instances.

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* Generous supplies of these drugs were furnished us by Merck & Co., Hoffman LaRoche Company, and Smith, Kline & French Company, respectively.

Pulse Rate and Blood Pressure. The pulse rate rises appreciably (except in the cases of block) within 1 to 2 minutes after the drug is given. Simultaneously with this rise, the blood pressure falls (Charts I, II III). The percentage rise in pulse rate (except in Cases 15 and 16 which were given obviously inadequate dosage) varied from 10 to 67, the average rise being 37%. The percentage fall in blood pressure in those cases in which this measurement was taken varied from 10 to 50, the average fall being 22%. In general, it may be stated (1) that the extent of drop of blood pressure was not quite as great as the rise in pulse rate; (2) that the greatest drop in blood pressure occurred in those cases which showed the greatest rise in pulse rate.

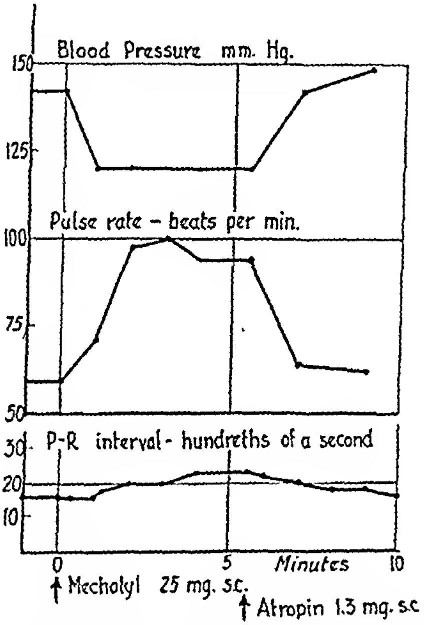

CHART I.—J. M. The effect of atropine sulphate following previous administration of mecholyl. The mecholyl has caused tachycardia and prolongation of the *P–R* interval. Following atropine the heart rate and *P–R* interval becomes essentially normal.

P–R Interval (Figs. 1 and 3). The *P–R* interval which varied from 0.16 to 0.22 second at the beginning of the experiment increased in almost every instance within 1 minute after administration of the drug, the maximum increase occurring within 2 to 4 minutes after the drug was given. In some cases intervals of 0.34 to 0.40 second developed. The average percentage increase in *P–R* interval was 46%. This prolongation of conduction time became even more strikingly evident when the ratio of the *P–R* interval to the total cardiac cycle (*PR*:TCC) were analyzed. In certain cases, so great did the *P–R* interval become in relation to the entire cardiac cycle that there was actual encroachment of the *P* wave on the preceding ventricular complex (*T* wave) (Cases 1, 8,

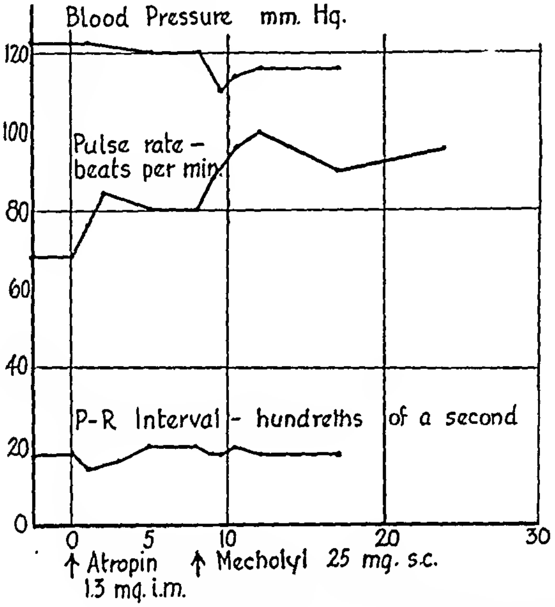

CHART II.—M. D. Effect of mecholyl when given after the previous administration of atropine. Tachycardia of mecholyl still occurs despite the absence of all the other mecholyl phenomena.

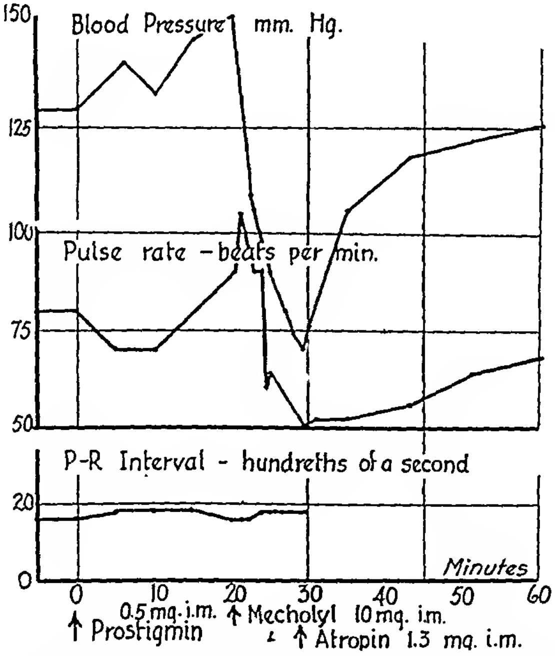

CHART III.—E. B. (See Fig. 6). Effect of small doses of prostigmin and mecholyl illustrating that bradycardia may be produced without heart block.

9 and 12). This was particularly striking in the case of John B. (Cases 13, 14, Fig. 1) in which as the *P–R* interval gradually became longer and the heart rate faster, there was further and further encroachment of the *P* wave upon the preceding *T* wave until finally the *P* wave merged with the *T* wave and became "buried" in it. During this stage, when the auricular complex occurred within the ventricular cycle, an occasional dropped beat developed. The "unloosening" of the *P* wave from the *T* wave when the *P–R* interval became gradually lessened is also brought out in the accompanying electrocardiograms. Ordinarily no definite changes in either the *P* wave, the *QRS* complex, or the *T* waves were discernible, although occasionally the *QRS* became slurred or the *S T* segment depressed (Cases 1, 12).

Rhythm. The rhythm usually remained regular after mecholyl administration. There was no evidence of sinus arrhythmia. Sinus tachycardia was the rule. In several cases, abortive *QRS* complexes became evident. In only one case did a severe degree of heart block develop with the doses of mecholyl used in our experiments.

Case Report. (J. H.) This patient seemed unusually sensitive to mecholyl administration, so that with 10 mg. of the drug, the reaction was as great or greater than the reaction in most patients when 25 mg. were given (Chart II). When 25 mg. of mecholyl were given on each of 2 occasions, incomplete and shifting heart block developed (Figs. 2*a*, *b*, 4); 22 seconds after administration of the drug the *P–R* interval had lengthened to 0.30 second. Then followed 4:1 block, 3:1 block, and 2:1 block in rapid succession. At times, complete block seemed present since ventricular complexes without preceding *P* waves were evident. Various changes in the *P* waves were present during this interval of about 2 minutes: diphasic *P*, notched *P*, and at times inverted *P*. The auricular rate during this period of block was constantly at 90 per minute, the ventricular rate varying between 42 and 72. After about 1 minute 2:1 block became the most usual phenomenon, although at intervals there were runs of tachycardia when the block was broken and the ventricle followed the auricle at each auricular impulse. The ventricular rate then averaged 60 to 72 per minute. Finally after 2 minutes of changing block, a normal sinus rhythm developed.

In another experiment, performed 1 week later, it was noted that electrocardiographic abnormalities developed almost immediately after injection of the drug (Fig. 4). In 20 seconds 2:1 block was evident. For a few seconds there was a run of ventricular fibrillation, followed by various types of block. Finally 2:1 block predominated with auricular rate of 100.

To summarize, the effects of mecholyl on the circulation as noted in these experiments, were as follows: (1) a slight fall in blood pressure; (2) moderate tachycardia; (3) a definitely or even markedly increased *P–R* interval and increased ratio of the *P–R* interval to the complete cardiac cycle; (4) exceptionally, in the doses given (25 mg.) varying degrees of heart block—2:1, 3:1, 4:1; (5) certain other inconstant and occasional changes, such as ventricular extrasystoles, ventricular fibrillation, widened and notched *P* waves, flattening of the *T* wave, and depression of the *S T* segment.

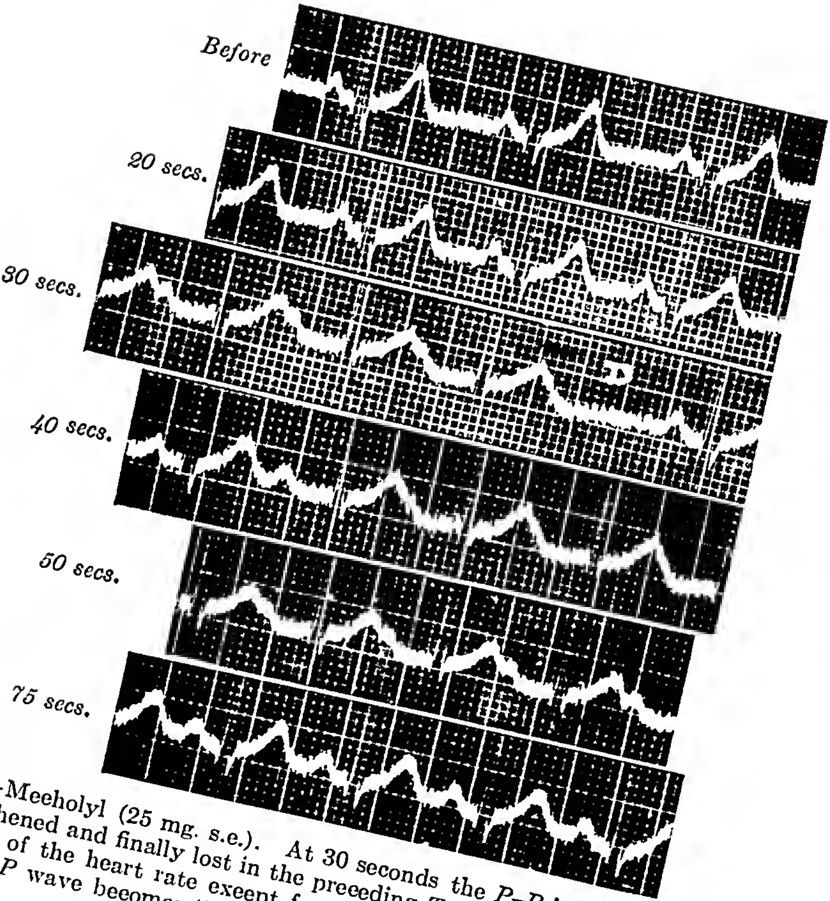
Before
20 secs.
30 secs.
40 secs.
50 secs.
75 secs.
D

Fig. 1.—Mecholyl (25 mg. s.c.). At 30 seconds the *P–R* interval becomes very much lengthened and finally lost in the preceding *T* wave. Simultaneously there is acceleration of the heart rate except for an occasional dropped beat (*D*). At 50 seconds the *P* wave becomes "unloosened" from the *T* wave; completely so at 75 seconds.

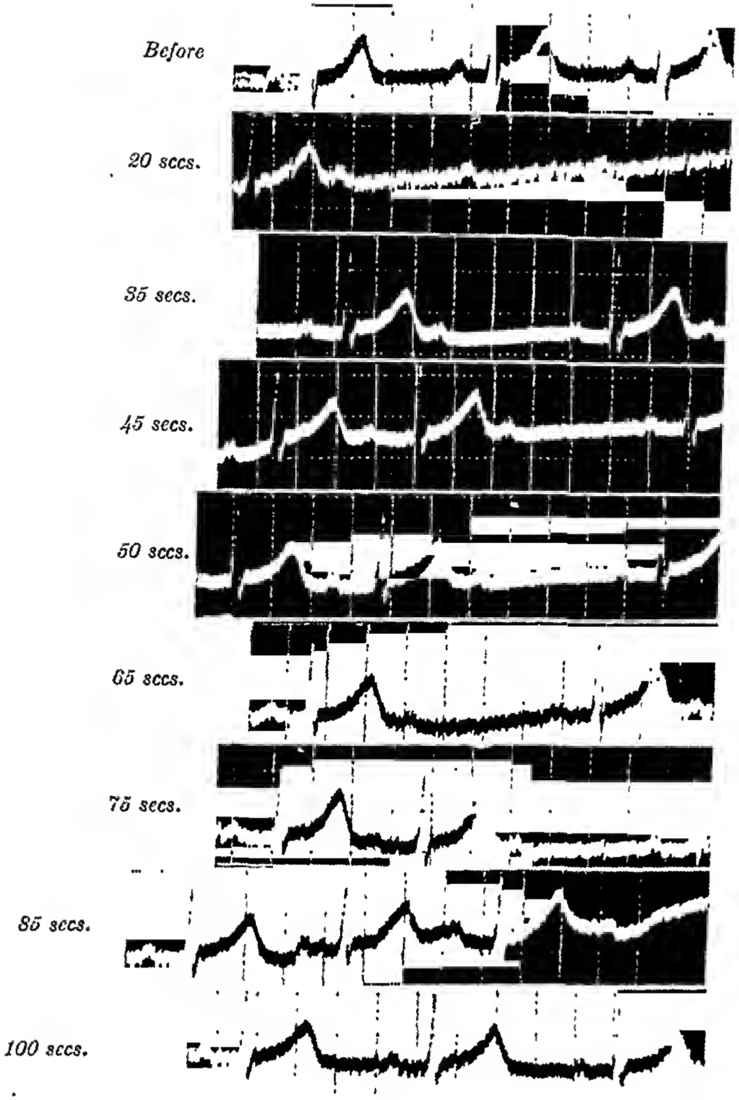
Before
20 secs.
35 secs.
45 secs.
50 secs.
65 secs.
75 secs.
85 secs.
100 secs.

FIG. 2.—Mecholyl (25 mg. s.c.) in a patient very sensitive to the drug. Twenty seconds following administration there is irregular block; at 35 seconds the block is mainly 2:1 in type; at 45 seconds there is tachycardia and lengthening of the *P–R* interval with occasional dropped beats. This is maintained during the next 35 seconds. Three seconds after atropine sulphate 1.3 mg. intravenously, the block disappears and the rhythm becomes regular.

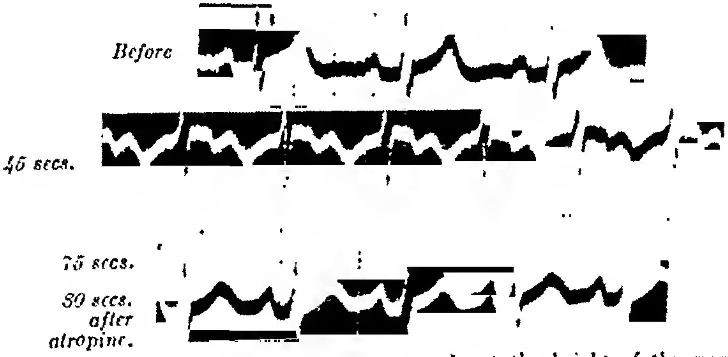
Before
45 secs.
75 secs.
30 secs.
after
atropine.

FIG. 3.—Atropine sulphate given intravenously at the height of the mecholyl reaction. Tachycardia and prolongation of the *P–R* interval 15 seconds after mecholyl is given. Thirty seconds after administration of atropine the *P–R* interval becomes very much shortened and possibly less than the control reading.

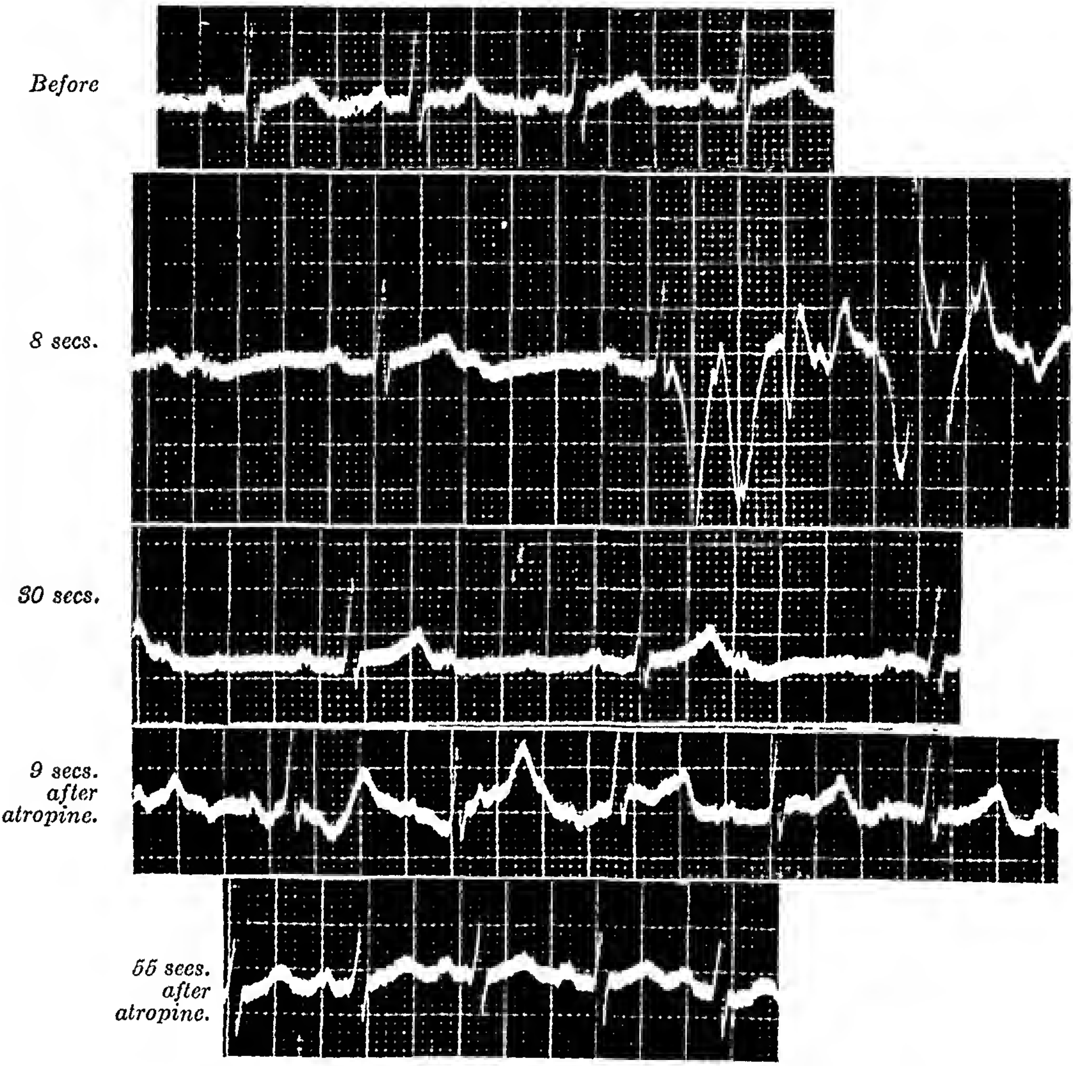
Before
8 secs.
30 secs.
9 secs. after atropine.
55 secs. after atropine.

Fig. 4.—Mecholyl (25 mg. s.c.) in the hypersensitive patient J. H. Thirty seconds after mecholyl, atropine sulphate (1.3 mg.) is given intravenously. Within 35 seconds after atropine administration the heart block has disappeared; within 55 seconds the *P–R* interval is normal. Note the run of ventricular fibrillation at 8 seconds after mecholyl.

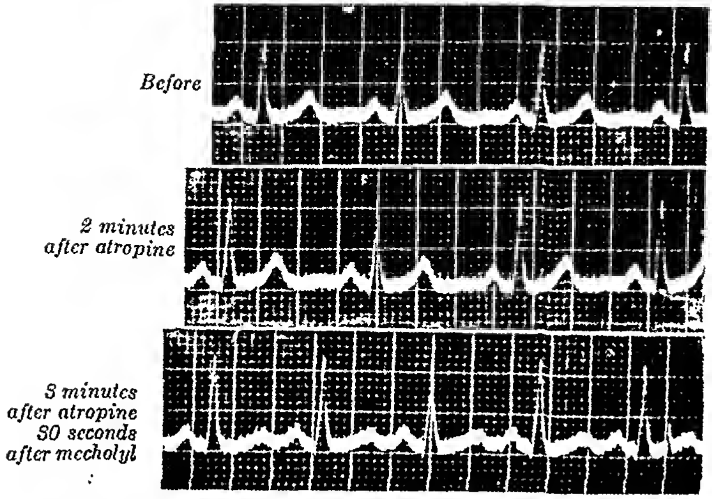
Before
2 minutes after atropine
3 minutes after atropine 30 seconds after mecholyl

FIG. 5.—Mecholyl administered after the previous injection of atropine. Note that (despite the absence of the various general effects of mecholyl) there is tachycardia and some prolongation of *P–R* interval, indicating that the atropine has not completely blocked the mecholyl effect.

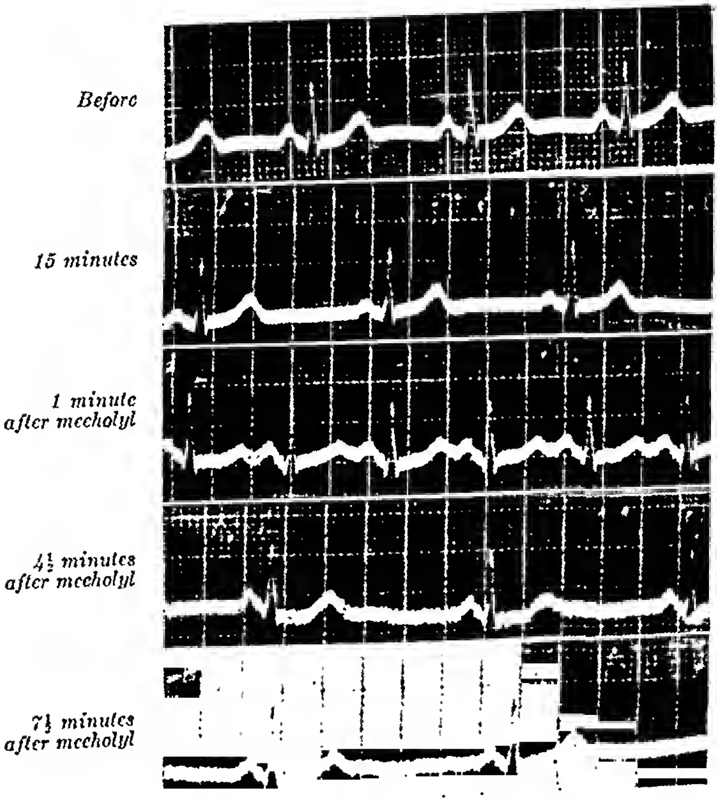
Before
15 minutes
1 minute after mecholyl
4½ minutes after mecholyl
7½ minutes after mecholyl

FIG. 6.—Prostigmin (0.5 mg.) and mecholyl (10 mg.) s.c. Bradycardia occurs after prostigmin administration without lengthening of the *P–R* interval, and tachycardia with slight lengthening of the *P–R* interval 1 minute after mecholyl is given. Bradycardia then occurs, becoming quite marked 7½ minutes after mecholyl is administered.

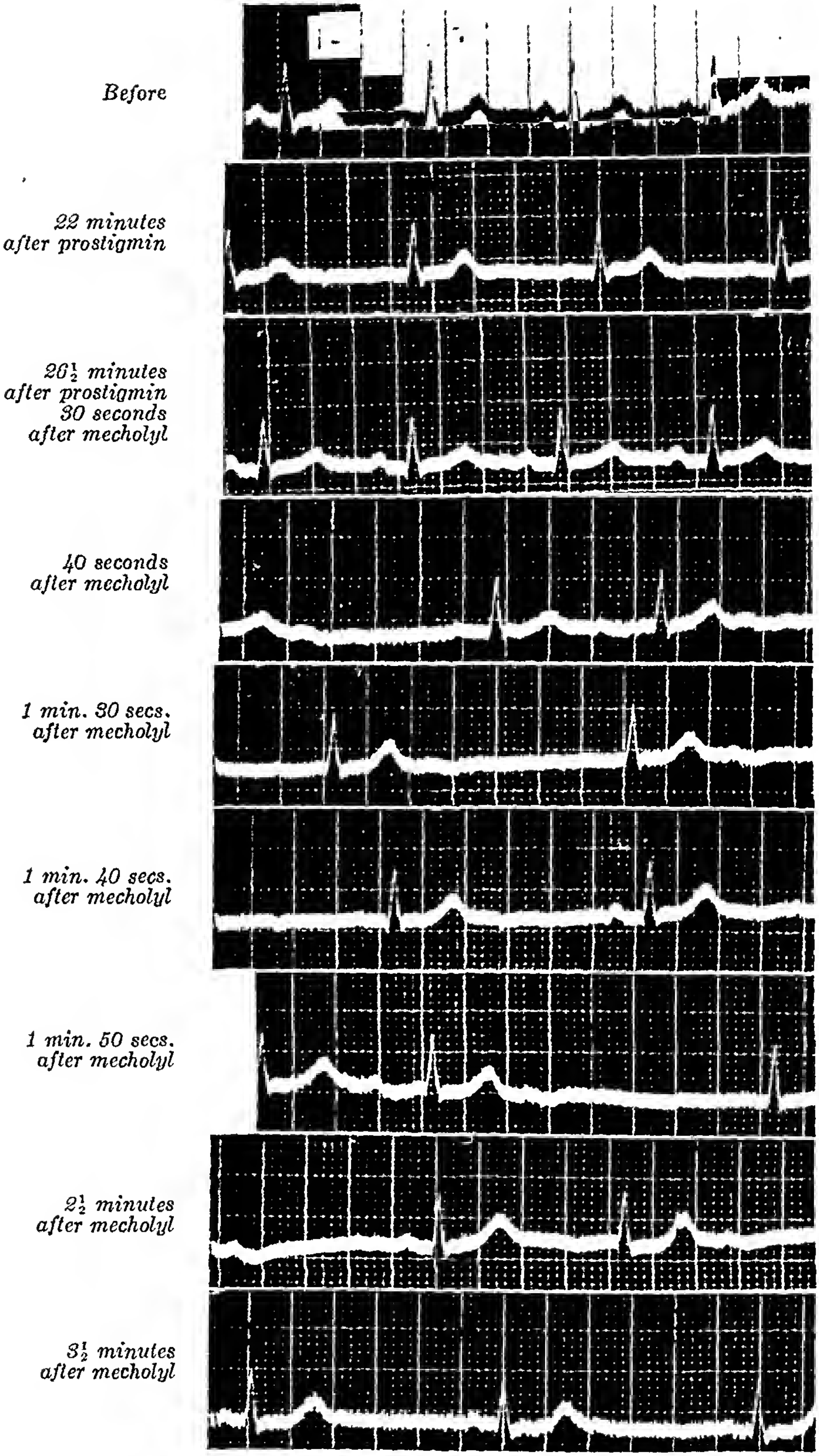
Before
22 minutes after prostigmin
26½ minutes after prostigmin 30 seconds after mecholyl
40 seconds after mecholyl
1 min. 30 secs. after mecholyl
1 min. 40 secs. after mecholyl
1 min. 50 secs. after mecholyl
2½ minutes after mecholyl
3½ minutes after mecholyl

FIG. 7.—Prostigmin (1 mg. s.c.) followed in 26 minutes by mecholyl (25 mg.). Bradycardia occurs after prostigmin administration without lengthening of the *P–R* interval. Thirty seconds after the administration of mecholyl the *P–R* interval is becoming lengthened, and at 40 seconds irregular block is present. One and one-half minutes after mecholyl the block appears to be complete at times. Note the inversion of *P* waves at 1 minute and 40 seconds after mecholyl, indicating ectopic auricular foci. The heart reverts to a regular rhythm with bradycardia 3 minutes and 30 seconds after injection of mecholyl.

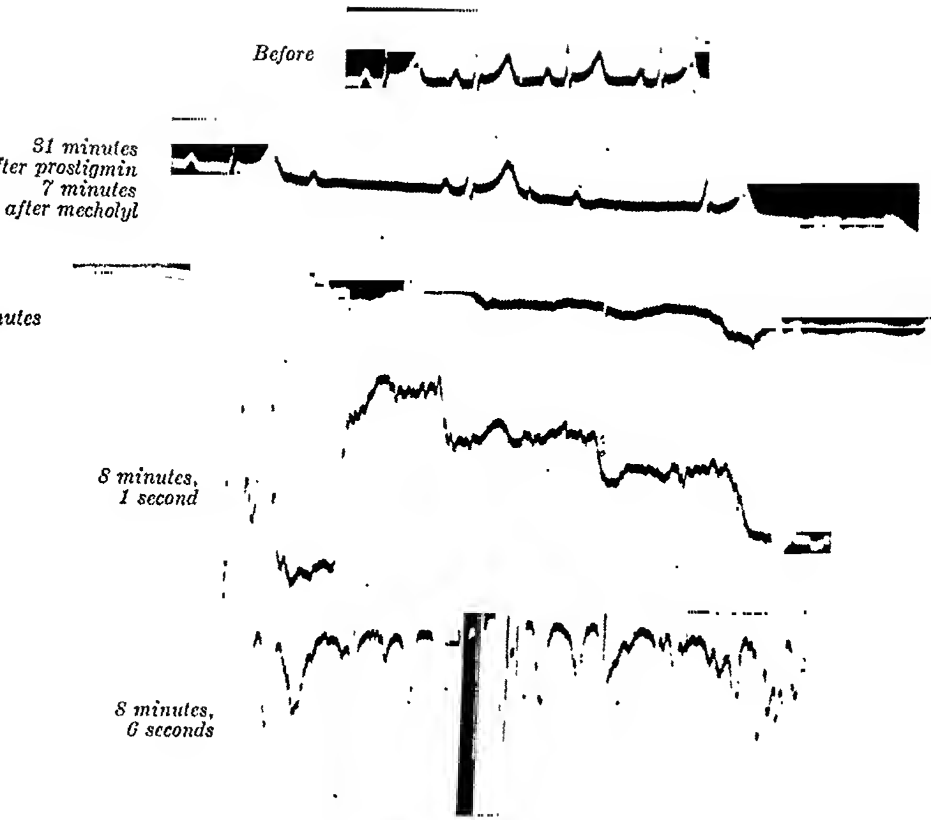
Before
31 minutes
ter prostigmin
7 minutes
after mecholyl
utes
8 minutes,
1 second
8 minutes,
6 seconds

FIG. 8.—Prostigmin administered subcutaneously 24 minutes prior to the injection of mechylol (15 mg.). Seven minutes after mecholyl is given there is almost complete block, and 8 minutes after there is almost complete asystole during which the patient was in collapse and pulseless. Atropine sulphate was administered intravenously together with benzedrine sulphate, following which the patient developed auricular and ventricular fibrillation and made complete recovery.

Prostigmin and Prostigmin Followed by Mecholyl (Figs. 6, 7, 8). Previous experiments have demonstrated the marked synergizing effects of prostigmin given previous to mecholyl administration and have shown that a very small dose of mecholyl, without effect alone, will cause the typical effects of a large dose of mecholyl if prostigmin is previously administered.

Prostigmin. Prostigmin was given in 5 cases in dosage of 0.5 to 1.5 mg. without demonstrable change in the blood pressure; in every case there was a definite lowering of the pulse rate. Although bradycardia developed, there was no definite change in the *P–R* interval. Other slight changes occurred in the electrocardiogram: slightly notched *P* wave in one, slightly flattened *P* wave in another higher *T* wave in third case. In general, prostigmin caused very little demonstrable effect on the circulation.

Prostigmin Followed by Mecholyl. A preliminary dosage of prostigmin of 0.5 to 1 mg. was followed by varying doses of mecholyl in 6 cases. The resulting effects varied not so much with the dosage of prostigmin as with the secondary dose of mecholyl. In Case 6, given 0.5 mg. of prostigmin followed by 2 mg. of mecholyl 16 minutes later, there was no change whatever in the pulse rate and the *P–R* interval. The blood pressure rose from 114/84 to 134/92. In Cases 1 and 5, 5 mg. of mecholyl were given after preliminary doses of 0.5 and 1 mg. of prostigmin respectively. In both of these cases, the cardiac rate rose rather markedly within 30 seconds to 2 minutes after mecholyl administration. With this rise in cardiac rate, there was a moderate drop in blood pressure and a slight although definite increase in the *P–R* interval.* Case 3 (Fig. 6) given 10 mg. of mecholyl after a previous dose of 0.5 mg. of prostigmin was interesting in that, after a preliminary rise in the cardiac rate from 60 to 105, marked slowing occurred within 6 to 8 minutes, the heart rate diminishing to 50 per minute. The blood pressure, which had risen from 132/86 to 156/82 after prostigmin, fell markedly when mecholyl was given and reached a low level of 70/40 10 minutes after the second drug was given. The *P–R* interval was practically unchanged during this period of bradycardia. The *T* wave became slightly flattened during this period but otherwise there were no changes.

In 2 cases previously given prostigmin, mecholyl was given in the usual dose of 25 mg. The results were so striking, withal so drastic, that further experimentation with these dosages was thought inadvisable.

In Case 4 (Fig. 7), 26 minutes after a dose of 0.5 mg. of prostigmin, 25 mg. of mecholyl were given subcutaneously. In 30 seconds, the heart rate had risen from 66 to 88 per minute. At the 40-second interval the *P–R* interval increased from 0.20 to 0.24 second. At 42 and at 44 seconds, dropped beats occurred, following which all the various types and gradations of shifting heart block were present for 3 minutes. Complete block at first occurred and lasted for about $1\frac{1}{2}$ minutes. During this time the *P* wave was frequently depressed or inverted. The ventricular rate during this period ranged from 36 to 48, the auricular rate from 57 to 63 per minute. During the next 2 minutes, ventricular contractions at times occurred without previous *P* waves, and *P* waves were frequently depressed, suggesting a continuation of the idio-ventricular (and auricular) rhythm. Finally, at approximately $3\frac{1}{2}$ minutes there was reversion to normal rhythm, although at a slow rate (sinus bradycardia) 54 per minute.

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* These considerations of pulse rate and blood pressure are taken up more fully in another paper on the synergism between prostigmin and mecholyl.

Case 2 was given 1 mg. of prostigmin subcutaneously (Fig. 8). No perceptible clinical changes occurred during this period and the heart rate was only slightly slowed: from 84 to 72 per minute. At the end of 24 minutes, 25 mg. of mecholyl was given subcutaneously. At the end of 6 minutes, no change had occurred: the rate was still 72 per minute and the *P–R* interval was still 0.18 second. However, $\frac{1}{2}$ minute later, there was 2:1 heart block with a ventricular rate of 40 per minute. Thirty seconds later, at the 7-minute interval, complete block developed. At first shifting block occurred: 2:1, 3:1, 4:1, with shifting *P–R* interval. Finally complete block developed with a ventricular rate of 35 (auricular rate 60) per minute. The patient at this period became extremely uncomfortable, sat up, and vomited profusely. The "beam" wandered completely off the record and the tracings became illegible for about a minute. Following this, there was total arrhythmia, which appeared to be ventricular fibrillation. Eight minutes after mecholyl was given, the patient went into collapse, the pupils were widely dilated, the pulse was imperceptible, and respirations ceased. No records were obtained during this period, the physicians being occupied in injecting first atropine sulphate 1 mg. and then benzedrine sulphate 25 mg. Fortunately, a few seconds after these drugs had been given, a short strip was taken on the electrocardiogram. At first, this showed complete heart block with the *QRS* complexes of extremely low amplitude. Then followed a period of complete asystole which lasted for 7.5 seconds, and during which neither auricular nor ventricular complexes were recognizable. Recovery then began, heralded by *P* waves at irregular intervals, and then finally an occasional very small ventricular complex. Many auricular waves then appeared in succession for about 2 seconds (probable auricular fibrillation) followed by an interval of ventricular fibrillation lasting about 30 seconds. The electrodes became disconnected at this period. Finally, about 3 minutes after atropine had been given, the pulse became perceptible and the patient made an uneventful recovery.

Atropine (Figs. 2, 3, 4, 5). Atropine sulphate was given either subcutaneously or intravenously and always in dosage of $\frac{1}{50}$ grain (1.3 mg.), although this dose was repeated in one case.

Atropine Administered Alone. The effects of the drug when administered alone were studied in 3 cases. In Case 1 there was slight rise in cardiac rate and a diminution within 1 minute of the *P–R* interval from 0.18 to 0.14 second. In Case 3, there was no change in the heart rate and only questionable change in the *P–R* interval. The blood pressure was not affected.

Atropine Following Previous Administration of Mecholyl. Mecholyl as the primary drug was followed in 6 cases by atropine sulphate given either intramuscularly or intravenously. The cessation of all the symptoms of the clinical effects produced by the use of atropine is a striking phenomenon which has been described elsewhere. An extremely rapid effect resulted from intravenous administration of the atropine.

Pulse Rate and Blood Pressure. It would naturally be expected that mecholyl, a "parasympathetic stimulant," would slow the pulse and atropine, a "parasympathetic paralysant," increase it. However, in our experiments, as noted above, the pulse rate became accelerated with mecholyl. As a corollary to this phenomenon, when atropine was given during the period of mecholyl tachycardia, actual slowing of the pulse rate occurred (Cases 3, 5, and possibly 4, Chart III). In the other 3 cases, no definite change in the pulse rate occurred except that in Case 1, in which 2:1 heart block was present with a ventricular rate of 50, the pulse rate rose first to 120 in 30 seconds and then slowed to 104 in 2 minutes.

The effects on the blood pressure were rather uniform. Following mecholyl, there was always a fall in pressure as noted above. Within 1½ to 2 minutes after atropine was given, however, there was a sharp and sudden rise in blood pressure which in every case observed became higher than its original level. In the 2 cases in which records of the blood pressure were taken for several minutes after atropine was given, there was gradual drop in pressure from the immediate high level to a normal level.

P–R Interval and Cardiac Rhythm. The *P–R* interval, which in every instance had become lengthened as the result of previous mecholyl administration, became appreciably and at times markedly shortened *within 30 seconds* after atropine was administered. Further slight shortening took place within the next few minutes in some of the cases. In Case 1, with 2:1 heart block, the heart became completely regular with *s-a* tachycardia within 30 seconds after atropine was given intravenously; in Case 5, with occasional dropped beats and *P* waves encroaching on the *T* complex (*q.v.*), there was almost immediate reversion to a completely regular rhythm when atropine was given.

Atropine Followed by Mecholyl. In 3 cases previously atropinized, 25 mg. of mecholyl were given within 7 to 12 minutes. In every case, a definite rise in heart rate occurred within 2 minutes after mecholyl was given. This was accompanied by the above mentioned characteristic effects of mecholyl on the cardiac mechanism (Fig. 5). None of the other clinical phenomena of the mecholyl reaction were present, except possibly for a slight flush over the face and chest. No sweating, salivation, rhinorrhea or lacrimation took place.

Atropine and Prostigmin. In one case, atropine was given following the previous administration of 1.5 mg. of prostigmin. The bradycardia produced by the prostigmin was transformed within 1 minute to the normal heart rate of 88 per minute. The *P–R* interval which had not been affected by the prostigmin became diminished following atropine administration.

In one case, both atropine and prostigmin were given 26½ minutes before administration of 25 mg. of mecholyl (Chart IV). No clinical effects were noted although at a previous experiment on the same patient (H. H.) complete heart block had developed when mecholyl was given following the previous administration of prostigmin. The heart rate became slightly elevated, the *P–R* interval became unchanged, and there was slight increase in *PR:TCC* ratio.

Benzedrine. The effects of benzedrine on the pulse and blood pressure have received consideration in a previous publication.[19a] With the dosage of benzedrine ordinarily used in our experimentation (30 to 40 mg.), the pulse rate is only slightly affected and may even become somewhat slowed. The striking effect is upon the blood pressure which almost always becomes elevated, frequently to marked degree. In the present group of experiments, particular attention was paid to possible effects upon the ECG.

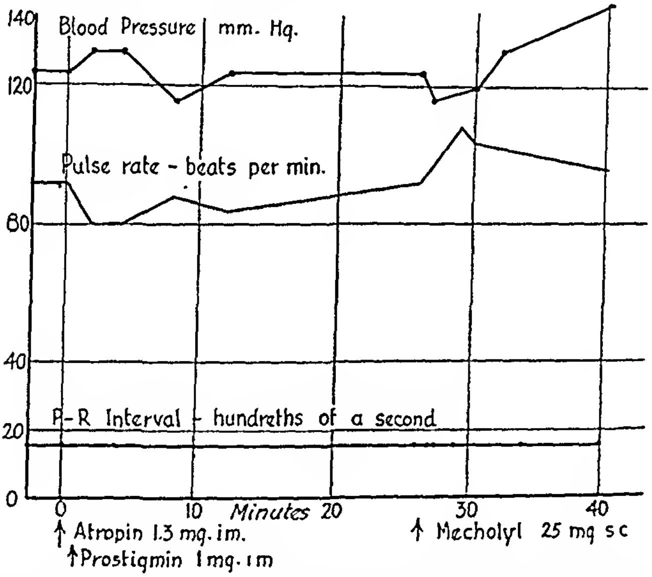

CHART IV.—H. H. The effect of atropine when given prior to the administration of prostigmin and mecholyl with resultant complete absence of the mecholyl effect except for tachycardia.

Benzedrine sulphate was administered as the only drug in 6 cases. In Case 1 (C. P.), given 40 mg. of benzedrine subcutaneously, the heart rate became somewhat slowed—from 88 to 66 while the blood pressure rose from 116/80 to 164/98. The *P–R* interval was possibly somewhat diminished, the voltage of the *T* wave in Lead II became definitely increased from 0.3 to 0.5 MV., and a prominent *U* wave became apparent. Otherwise no changes occurred. In Case 2 (D. F.), also given 40 mg. of benzedrine sulphate subcutaneously, no changes whatever occurred in the *P–R* interval or in the voltage of the various waves although there was a marked rise in blood pressure from 118/80 to 172/100. In Case 3 (J. S.), given 30 mg. of the drug, the cardiac rate became increased from

72 to 100 per minute, the blood pressure rising only slightly—from 100/60 to 130/80. The *P–R* interval was essentially unchanged (0.50 to 0.45 second). The *T* wave in Lead II became definitely diminished in voltage from 0.6 to 0.35 MV., one ventricular extrasystole was seen but otherwise no changes occurred.

Previous experimentation had shown that atropine enhances the sympathetic effect of benzedrine. Accordingly, in one case (G. S.) atropine sulphate, gr. $\frac{1}{50}$ (1.3 mg.), was given simultaneously with 20 mg. of benzedrine sulphate. The blood pressure rose from 122/84 to 150/110 and the pulse rate from 64 to 108 per minute. Aside from a slight diminution in the voltage of the *T* wave in Lead II, no changes occurred in the electrocardiograms. In another case, prostigmin, 1 mg., was given together with benzedrine sulphate 40 mg. The *P–R* interval became somewhat shortened—from 0.16 to 0.12 to 0.14 second and a prominent *U* wave became apparent in Lead II after 41 minutes. Otherwise, no essential changes were noted.

In summary, the few experiments carried out with benzedrine sulphate demonstrated very little effect on the electrocardiogram in the doses used. The *T* waves were slightly affected and a prominent *U* wave became apparent in 2 cases.

Discussion. I. ESSENTIAL PHYSIOLOGY AND PHARMACOLOGY. As the actions of these various chemicals have been presented elsewhere,[16–19b] they will not be presented here in detail.

It has been abundantly shown that sympathomimetic or adrenergic drugs (adrenaline, benzedrine) act like sympathin—on the second synapse of the sympathetic nervous system, while parasympathomimetic (or cholinergic) drugs act on the myoneural and tissue connections of the vagus (and possibly on the first synapse of the sympathetic system[2,6a,b,c,7a,b,14,15]). Physostigmin (and prostigmin) have special actions which ultimately become cholinergic. According to the most recent conceptions,*[9,25] these drugs inhibit the enzymic activities of the esterases and thus enhance the effects of the normal concentrations of acetylcholine which are already present. Atropine by acting on the myoneural junctions in the tissues prevents acetylcholine from permeating the cell membrane with resultant loss of its characteristic effects.

The heart may be said to be delicately poised between two opposing chemical mechanisms.[5,10] On the one hand is the accelerator mechanism activated through the sympathetic system; on the other, is the "decelerator" or "brake" mechanism which is innervated through the medium of the vagus nerve. It is likely that the terminal myoneural junctions are present not only in the sino-auricular node but in the auricles themselves, the auriculoventricular node, the bundle of His, and the entire Purkinje system. Both sympathin and acetylcholine bring about their ultimate effects by acting on these widely distributed junctions.

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* *Cf.* Refs. [6a,b,c], 14, 15.

II. Analysis of the Experimental Results. 1. *Mecholyl.* The two outstanding effects of mecholyl on the heart as shown by the electrocardiogram were tachycardia and prolongation of the conduction time between the auricle and ventricle.

(*a*) *Tachycardia.* Since this drug is conceded by most investigators to be the most active and the purest example known of a parasympathomimetic drug,[11a,b,22] the tachycardia which develops almost constantly seems paradoxical. In animal experimentation, furthermore, investigators have usually described bradycardia rather than tachycardia.[4] This is probably explainable by the relatively large dosage of drug used in animal experimentation with the probable production of complete heart block. In one case not reported above, a patient was mistakenly given 150 mg. of mecholyl rather than the usual dose of 25 mg., with the result that complete block (not recorded by electrocardiogram) developed within a few seconds. The ordinary dosages given in our experiments, although considered relatively large for human administration, are very much smaller per unit of body weight than in animal experiments and therefore productive possibly of somewhat different effects.

The cause of the tachycardia is obscure. If the drug is really vagomimetic, bradycardia should develop. One may speculate on the possible reasons for the tachycardia. Is it due (1) to the drop in blood pressure which occurs coincidentally with the rise in heart rate; (2) to an acetylcholine effect on the sympathetic (accelerator) nerves to the heart, or (3) is it a nicotine effect?

1. The drop in blood pressure takes place coincidentally with the rise in pulse rate, and it is usually true that the greater the drop in pressure, the greater is the tachycardia. A study of the percentage drops in blood pressure and rises in heart rate shows that the rise in heart rate is usually greater than the fall in blood pressure and often much greater. In certain instances a definite tachycardia was present without definite fall in pressure.

2. If it is correct that acetylcholine is liberated at the first synapse of the sympathetic system,[7a,b] then the injection of acetylcholine might enhance the ordinary acetylcholine activity at this synapse and thus result in stimulation of the accelerator sympathetic fibers. That this might be the case is indicated in the electrocardiograms in which the tachycardia is seen to be of the "sinus" type denoting direct stimulation of the accelerator activity of the sino-auricular node. This is also confirmed by the results of mecholyl-atropine administration. The tachycardia induced by mecholyl was not abolished by the dosages of atropine used in our experiments (1.3 to 2.6 mg. or $\frac{1}{50}$ to $\frac{1}{25}$ gr.) although all the clinical effects such as perspiration, salivation, rhinorrhea, etc. could be prevented even with the use of only 0.065 mg. ($\frac{1}{1000}$ gr.). This tachycardia was present despite the fact that following the use of atropine, a sharp rise in blood pressure took place. This phenomenon not only militates against the theory that the tachycardia induced by mecholyl

is due to a fall in blood pressure, but almost certainly points to the conclusion that this phenomenon is divorced from the parasympathetic nervous system and related to a direct action of mecholyl on the sympathetic or accelerating mechanism of the heart.

3. Acetylcholine, which has been actively studied for many years, was universally thought to have a double effect: a "muscarine" action paralyzed by atropine and a "nicotine" action.[13a,b] The muscarine action is the typical one of the vagus, whereas that of nicotine is a mixed and complicated one, especially on the circulation, since it may not only cause stimulation of the accelerator ganglia but may also slow the heart, depending to great extent upon the dosage employed.[5] In this respect, mecholyl recalls the nicotine type of reaction and it is possible that this drug does not have a pure muscarine type of effect, but may also have a few of the effects of nicotine in small dosage.

(b) *Prolongation of A–V Conduction Time.* The second striking effect of mecholyl administration is the increased conduction time between auricle and ventricle. Various gradations in results occur although the results obtained in the same patient on different days were astonishingly uniform. Only one patient of our series given the ordinary dosage of mecholyl developed greater degrees of heart block. As noted above, this patient appeared to be unusually sensitive to mecholyl administration.

(c) *Other Changes.* In no instance in our series of cases given mecholyl alone was an arrhythmia produced, other than that due to heart block, although very small ventricular extrasystoles were at times seen and ventricular fibrillation in one very sensitive case. Neither sinus arrhythmia, as noted by Starr, Elsom, Reisinger, and Richards,[24] nor auricular fibrillation, as noted by Nahum and Hoff[20] in their hyperthyroid patients, developed. The latter investigators felt that since they were able to induce transient auricular fibrillation in 5 patients given large doses (50 mg.) of mecholyl, one of the factors in the spontaneous production of auricular fibrillation was the action of the vagus nerves on the heart. Since auricular fibrillation did not develop in normals given either mecholyl or an electric shock, Nahum and Hoff postulated that fibrillation is due to the simultaneous action on the heart of two factors (1) the vagus nerves, and (2) an "E" irritating factor. These conclusions may possibly be criticized in that the action of the vagus is not necessarily that of mecholyl, since discrepant actions are sometimes noted; and furthermore the accelerator stimulating effect induced by mecholyl may have been so much greater in hyperthyroidism than in the normal that the circus motion of auricular fibrillation rather than the regular rhythm of *s-a* tachycardia might have been set up in the auricle.

In summary, the chief cardiac effect of mecholyl is a "dromotropic" one due to its action on the conducting mechanism; this may become a "chronotropic" effect if severe grades of heart block develop, but ordinarily tachycardia is present. There may be an "inotropic" action on the heart muscle as evidenced by the presence of abortive ventricular extrasystoles and minor changes in the *T* waves. The vagal slowing ("chronotropic") effect due to a direct action on the *s-a* nodes seems to be entirely lacking (*Cf.* Armstrong.[1]) In work with acetylcholine on the hearts of eels and turtles, Fischer[8] demonstrated that this drug had little influence upon the pacemaker and upon the size of the movements of the right vena cava, even though the conduction to the auricles might be completely blocked. He concludes that vagal stimulation probably causes the release of different chemical transmitters depending upon the points at which the nerves terminate.

2. *The Synergistic Effect of Prostigmin on the Mecholyl Reaction and the Blocking Effect of Atropine.* For many years the assertion was simply made that physostigmin was a parasympathetic stimulant and therefore resulted in such typical parasympathetic effects as salivation, perspiration, increased intestinal motility and the like, although it was recognized that these effects were not always typical of parasympathetic stimulation. In recent years an entirely new conception of the action of physostigmin has been elucidated. This concept rests upon the assumption that enzymes called "esterases" are normally present in the tissues in close association with the myoneural junctions and cells where acetylcholine is liberated. These esterases seem to be active in the constant destruction of acetylcholine and apparently prevent its accumulation in the tissues. According to many recent investigations, physostigmin (and prostigmin) inhibit the activity of the esterases and thus allow the full acetylcholine effect. Thus the action of physostigmin is in reality the action of acetylcholine which is "unmasked" or released by the inhibitory or neutralization effect upon the esterases.

In the electrocardiogram, the effect of the drug when given alone was to produce slowing of the heart, apparently by a direct action on the *s-a* node since no change in the *P–R* interval took place. When the ordinary doses of mecholyl were given following an initial injection of prostigmin, the full effects of extreme dosage with mecholyl were evident: complete and incomplete heart block, collapse, etc. When mecholyl was given in small doses after an initial injection of prostigmin, the typical effects of a large dose of mecholyl developed: tachycardia, prolongation of the *P–R* interval. This was not always true, however, since when a small dose of prostigmin was followed by a relatively small dose of mecholyl, marked bradycardia might develop after an initial and fleeting tachycardia. It may be stated, then, that prostigmin allows the development of a full or pure acetylcholine effect.

Atropine inhibits the effect of prostigmin on the *s-a* node and also completely prevents (except for slight tachycardia) the mecholyl effects of the prostigmin-mecholyl combination. Atropine would thus appear to act upon the nerve endings of the vagus supplying both the *s-a* node and the conducting bundle. In the presence of the inhibitory or blocking effect of atropine, acetylcholine cannot act and thus the three characteristic effects of the vagus on the heart (chronotropic, dromotropic, inotropic) are lost. This results in: (1) tachycardia; (2) shortening of the *P–R* interval; and, (3) rise in blood pressure.

3. *Benzedrine.* Benzedrine sulphate, a sympathomimetic drug, has a far "gentler" and more sustained effect than the related drug adrenalin. Its effects upon the blood pressure were much more constant and striking than upon the electrocardiogram in which only minor changes in voltage, principally of the secondary ventricular waves, were noted. No definite effects either upon the *s-a* node or the conducting bundle could be elicited.

III. CLINICAL IMPLICATIONS. The clinical implications are numerous. It has long been known that cases of marked bradycardia, partial heart block, and even of complete block may at times be on a "functional" basis, the heart apparently being normal except for its rhythmic disturbance. That this might be due to an enhanced vagal effect has long been suspected. The production of bradycardia, increased conduction time between the auricle and ventricle, and of various grades of severe heart block *in normal individuals*, by the use of the chemical mediator of the vagal impulses indicates that the heart block of certain—chiefly young—individuals is probably due to a vagal, *i. e.*, an acetylcholine, effect.

The therapeutic implications of the drugs we have studied easily suggest themselves. Starr and his co-workers[23a,b] have already utilized mecholyl extensively in the clinic, particularly in paroxysmal auricular tachycardia. Personal observation of the use of this drug has convinced us that it is frequently a dangerous one to use, particularly in the elderly. Sufficient emphasis does not appear to have been placed upon the constant and often quite marked tachycardia which follows the use of the drug in its ordinary dosage. This together with the sudden drop in blood pressure may prove a positive deterrent to the use of mecholyl in these cases. It should be noted, too, that other studies have demonstrated an adverse effect upon the coronary circulation,[26] so that the use of mecholyl in those suspected of having coronary disease is probably contraindicated. The so-called "side-effects" of mecholyl should also be kept in mind. These are in reality just as much part of the mecholyl reaction as the effects on the heart. The extreme perspiration and especially the extreme salivation and increase in the bronchial secretion may prove very distressing. In any event, the striking effect of even such small doses as 25 mg. of mecholyl upon the healthy, vigorous young male should make the clinician wary of its use in those affected with heart disease.

Better results in cases of severe tachycardia may possibly be obtained by the judicious combination of small doses of prostigmin and *small doses* of mecholyl. We wish to make it clear that these drugs should not be used unless their effects have been thoroughly studied and understood. The drastic actions of the prostigmin-mecholyl combination are worthy of great respect. However, the careful clinician should not be deterred from using a relatively small dosage (say 10 mg.) of mecholyl after 0.5 mg. of prostigmin. With this combination, marked bradycardia and moderate prolongation of the *P–R* interval *may* be obtained, although if a complete blocking effect is desired, as in paroxysmal auricular tachycardia, a full dose of 25 mg. of mecholyl may be necessary. At all events, whenever mecholyl or prostigmin-mecholyl is being used, *it is always necessary to have close by a syringe filled with a solution of atropine sulphate.* The dosage of atropine is not so important as its readiness for immediate use. Injection is preferably made intravenously, since by this route complete cessation of the mecholyl effect will be produced within 30 seconds in almost all cases. If the injection is given subcutaneously, 2 to 4 minutes may supervene before the reaction is terminated.

It is possible that prostigmin given alone in sufficient and frequent dosage may prove of some value in causing diminution of heart rate without the use of mecholyl. This would of course be preferable since there is no reduction in blood pressure, no perspiration or salivation, and most important of all, no complicating tachycardia.

The effects of mecholyl in lowering the blood pressure have naturally resulted in its use in hypertension, so far without effect except a very temporary one of about 15 to 30 minutes. Whether the procedure of iontophoresis more or less continuously applied might prove helpful in this regard is still subject to future investigation. In some of our other experiments, chiefly on the gastric juice, iontophoresis with mecholyl resulted in continuous achlorhydria and mucin production for 60 to 120 minutes. The procedure of iontophoresis with mecholyl has already proved helpful in the treatment of vacular disorders of the extremities and possibly in chronic atrophic arthritis. Again, it should be reiterated that even in these conditions, the so-called side effects of mecholyl should constantly be kept in mind particularly when the procedure is utilized in the elderly and in those with suspected coronary disorders.

The effects of benzedrine on the circulation, particularly in shock, peripheral circulatory collapse, and following the use of intravenous amytal anesthesia have already been cited in a previous article. Because of its hypertensive effect, benzedrine may also prove useful in the severe hypotension of peripheral circulatory failure and that following spinal anesthesia.

Summary and Conclusions. 1. Mecholyl (acetyl-beta-methylcholine chloride), prostigmin, atropine, and benzedrine, acting chiefly on the autonomic nervous system, were studied for their effects on the normal human circulation. Particular attention was paid to electrocardiographic changes.

2. Mecholyl in the dosage ordinarily used (25 mg.) causes a fall in blood pressure, tachycardia, and an increase in the *P–R* interval. Atropine given intravenously causes immediate cessation of the mecholyl effects and when given prior to the administration of mecholyl blocks all of the mecholyl effects except the tachycardia.

3. Prostigmin given alone causes sinus bradycardia; when given prior to mecholyl administration, its effects depend upon the dosages utilized. A small dose of prostigmin followed by a small dose of mecholyl may cause marked sinus bradycardia; a small dose of prostigmin followed by the ordinary dose of mecholyl causes severe grades of heart block, at times complete. The synergistic effects of the prostigmin-mecholyl combination may be completely blocked by the prior administration of atropine. Benzedrine causes a marked rise in blood pressure, but only slight and inconstant "inotropic" effect on the heart.

4. The tachycardia of mecholyl is critically analyzed in the light of modern investigation on the chemical mediators of the sympathetic nervous system together with the electrocardiographic findings.

5. Certain clinical considerations present themselves. Slowing of the heart may regularly be produced by the careful administration of prostigmin and mecholyl. The use of this combination in paroxysmal auricular tachycardia may be of greater value than that of mecholyl alone. Benzedrine, because of its prolonged action in raising the blood pressure, may be of value in certain cases of peripheral circulatory collapse, postural hypotension, the hypotension of spinal anesthesia and of the barbiturates when administered intravenously.

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THE CAUSE OF DEATH IN CORONARY THROMBOSIS, WITH SPECIAL REFERENCE TO PULMONARY EMBOLISM.

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IN the extensive literature dealing with coronary thrombosis, the causes and modes of death have been defined[2,4,6] but little attention has been directed to their relative incidence. The frequency with which pulmonary infarction was found at postmortem examination in our patients who died of coronary thrombosis suggested that this complication might be more common than is generally believed. In order to determine the incidence of pulmonary infarction as well as other causes of death, the records of 200 consecutive cases of coronary thrombosis proven by autopsy, all of which were examined by the Department of Pathology of this hospital, were reviewed. They occurred between the years 1913 and 1936.

These cases were divided into 3 groups according to whether the death was sudden, due to congestive heart failure, or due to miscellaneous group of causes including systemic embolism (Table 1).

TABLE 1.—MANNER OF DEATH IN 200 AUTOPSIED CASES OF CORONARY THROMBOSIS.

Type.	Number of cases.	Per cent.
Sudden	64	32
Congestive heart failure	107	53.5
Miscellaneous	29	14.5

It is common experience for the fatal termination of the disease to be sudden. Usually there is no clinical evidence before death which would have suggested the imminence of such an event.[3,4] The accepted explanations for such abrupt deaths are ventricular fibrillation, complete heart block with a Stokes-Adams attack, and rupture of the heart. To this group of causes should be added massive pulmonary infarction. In this series, the majority of patients were stricken with the disease before coming to the hospital, were apparently doing well and then died suddenly and unexpectedly within a few minutes. We have used the term "sudden death" in this sense rather than applying it only to the group dying instantly. Such a rapid termination following coronary thrombosis may occur within a few hours or days after the onset, but may be delayed for a matter of weeks in the event of either pulmonary embolism or Stokes-Adams attack, or until a subsequent cardiac infarction occurs.

Of the entire group, 64 cases (32%) died suddenly (Table 2).

TABLE 2.—ANALYSIS OF CASES DYING SUDDENLY

Cause.	Number of cases.	Per cent of entire group.	Per cent of this group.
Possible ventricular fibrillation	34	17.0	53.1
Myocardial rupture	15	7.5	23.4
Pulmonary embolism	13	6.5	20.3
Stokes-Adams	2	1.0	3.1

Thirty-four of these (17% of the total) had insufficient pathologic changes in the heart or other organs of the body to account for the exitus and by inference it is assumed that these patients died of ventricular fibrillation. In 15 cases (7.5%), there was found a rupture of the myocardium. Only 2 patients died during a Stokes-Adams attack. In 13 (6.5%), the manner of death appeared similar to that produced either by cessation of effective heart action or by pulmonary embolism. Autopsy examination gave almost indisputable evidence in every case that pulmonary infarction was the probable cause of death since one or both of the main pulmonary arteries were obstructed by antemortem thrombi and the resulting area of infarction was extensive. In all of these cases, with one exception, passive congestion of the lungs was present before death, a fact which accounts for the rapidity with which the changes indicating pulmonary infarction occurred. The single exception was a case in which a very large embolus arose from the iliac vein.

As would be expected of a disease which so seriously damages the myocardium on one or more occasions, the commonest cause of death is congestive heart failure.[5,7] In this series of patients, 107 (53.5%) presented signs typical of cardiac decompensation both before and at the time of the terminal event and were considered to have died of this cause. It was not uncommon to find transient signs of congestive heart failure soon after the myocardial infarction occurred, but such cases were not included in this group. A few of the patients with cardiac decompensation had in addition signs of peripheral vascular collapse. This combination of signs occurred in those patients dying shortly after the cardiac infarction, but it seemed apparent that the element of congestive failure, mainly of the left ventricular type, played the dominant rôle in the cause of death.

While bronchopneumonia is the most frequent contributory cause of death in congestive heart failure, it was found that the occurrence of pulmonary embolism was another important factor in precipitating the exitus. Thus, in 35 (32.7%) of the cases with congestive heart failure, evidence of moderately extensive pulmonary infarction was found at autopsy. These pathologic findings suggesting that pulmonary embolism was the most important contributory cause of death were further validated by the clinical histories. Many of the patients showed typical signs and symptoms of pulmonary embolism, while in others the change in the clinical picture for the worse was so abrupt that the occurrence of this complication was the most reasonable explanation.

There were 29 patients (14.5%) who died of causes apart from or remotely related to the coronary thrombosis. In order of frequency these causes were as follows: bronchopneumonia, 7; cerebral hemorrhage, 6; carcinoma of the lung, 2; uremia, 2; postoperative shock, 2; septicemia, 2; peritonitis, 2; 1 case each of diabetic coma, ruptured mycotic aneurysm, acute pancreatitis. Only 3 patients of this series died as a result of systemic emboli; 2 of these were mesenteric and 1 cerebral.

Since the incidence of embolism in this series is surprisingly high when compared with the figure of 19.2% found by Parkinson and Bedford[8] and so that of 14.6% found by Conner and Holt,[1] it is of interest to deal more specifically with this complication. Of the 200 cases, 62 (31%) showed postmortem evidence of embolism. Only 49 (24.5%) of these (46 pulmonary, 2 mesenteric and 1 cerebral), as previously noted, were considered as either the main or the contributory cause of death. When the sites of infarction were studied, it was found that in 36 cases it was pulmonary alone, in 13 systemic alone, and in 13 both pulmonary and systemic.

The source of the pulmonary emboli was the interventricular septum in 17 cases, the right auricle or right auricular appendage in 18, and the pelvic or leg veins in 8. The systemic emboli had their origin in thrombi from the endocardial surface of the left ventricle in 20 cases and from that of the left auricle in 3. (In 4 cases emboli arose from 2 different sources which accounts for the apparent discrepancy in the total of 66 cases.)

Summary and Conclusions. A study of the causes of death in 200 autopsied cases of coronary thrombosis shows that 32% of the patients died suddenly, 53.5% died of congestive heart failure and 14.5% of other causes. Of this latter group, 2 died of mesenteric embolism and 1 of cerebral embolism.

In addition to myocardial rupture, ventricular fibrillation, and Stokes-Adams attacks, it was found that pulmonary embolism accounted for sudden death in 6.5% of the cases.

In 107 patients dying of congestive heart failure, pulmonary embolism was the most important contributory cause of death in 35 (32.7%).

Embolism occurred in 62 cases (31%), but in only 49 (24.5%) did this complication affect the outcome of the disease.

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(1.) **Conner, L. A., and Holt, E.:** Am. Heart J., 5, 705, 1929 1930. (2.) **Fulton, F. T.:** Ibid., 1, 138, 1925. (3.) **Lambert, A.:** Am. J. Med. Sci., 182, 769, 1931. (4.) **Levine, S. A., and Brown, C. L.:** Medicine, 8, 245, 1929. (5.) **Master, A. M., Dack, S., and Jaffe, H. C.:** Am. Heart J., 13, 330, 1937. (6.) **Nathanson, M. H.:** Arch. Int. Med., 58, 685, 1936. (7.) **Palmer, J. H.:** Quart. J. Med., 6, 49, 1937. (8.) **Parkinson, J., and Bedford, D. E.:** Lancet, 1, 1, 1928.

BOOK REVIEWS AND NOTICES.

INJECTION TREATMENT OF HERNIA. By CARL O. RICE, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Surgeon in Charge of the Surgical Out-Patient Department of the Minneapolis General Hospital, etc. With the assistance and coöperation of HAMLIN MATTSON, M.D. Pp. 266; 83 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, $4.50.

DR. RICE has prepared a compact monograph on the injection treatment of hernia, a subject which is forcing its way into recognition as an acceptable method of treating some forms of hernia. Chapters on the historical development of the injection method and on the classification of hernia precede the more important portion of the book. The author gives excellent and concrete discussions of the anatomy and the etiology of hernia, and in a short chapter points out the necessity and method of making a differential diagnosis, especially in the inguinal herniæ. The sixth chapter, devoted to the truss, is the only modern and concise discussion of its sort that is known to the Reviewer. A chapter on the technique of treatment of hernia by injection describes in detail the method used by the author and his associates. He describes the various solutions which have been used, illustrates the various points in the technique and discusses the immediate and late complications, giving methods of treatment. Then follows a description of the experimental work done by the author to demonstrate the development of fibrous tissue resulting from injections. The last chapter, a summary of the sections of workmen's compensation laws relating to hernia, does not seem to be related in any way to the injection treatment of hernia.

The book serves its purpose very well in that it gives the reader a clear picture of the history, method and results of the injection method of hernia treatment. It is well illustrated and will prove valuable to those who wish to treat hernia by this method. The author's experience makes the book authoritative.

L. F.

THE PRINCIPLES AND PRACTICE OF CLINICAL PSYCHIATRY. By MORRIS BRAUDE, M.D., Associate Clinical Professor of Psychiatry, Rush Medical College, The University of Chicago; Attending Psychiatrist, Cook County Psychopathic Hospital, Chicago. Pp. 382; 7 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.00.

THE purpose of the writer is to simplify the field of mental disease so it may be more readily grasped by the student of medicine, of social science and of jurisprudence. An important chapter and one frequently omitted from more pretentious works on psychiatry is Simulation; however, the meaning of this ruse should not be confined to the "feigning of illness;" for instance, those in mental hospitals frequently simulate sanity in the effort for release. The chapter on psychoanalysis is well written and its numerous definitions are an aid to the understanding of this controversial subject. In addition to the major psychoses, the psychoneuroses and mental deficiency are considered. Each chapter contains a bibliography that is helpful to the student desiring further enlightenment. It may be said the author attains his objective and that criticism for the most part can only be made in minor matters, such as the term, "criminally insane"—an impossible entity.

N. Y.

THE TRAFFIC IN HEALTH. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine; Lecturer in Materia Medica, Training School for Nurses, Jewish Hospital of Brooklyn. Pp. 393. New York: Navarre Publishing Company, 1937. Price, $2.75.

THIS book is a sermon for laymen on the subject of "patent" medicines and cosmetics, and bids for readers' attention by means of its dramatic title and striking dust-jacket. The information presented is similar to that contained in the American Medical Association's "Nostrums and Quackery," and dissemination of it would no doubt benefit the general public. Many familiar "patent" medicines are described as to composition, alleged action or therapeutic purpose, manufacturing cost, and retail price. A section on cosmetics presents similar information, and might be particularly disillusioning to the users of those preparations. There are several general discussions of therapeutic principles, dietetics, obesity, diabetes, tuberculosis, allergy, and the like. There is an extensive bibliography for readers who desire more information. The index is excellent, listing every reference to each nostrum. Numerous repetitions make the text prosy in spots. The proofreading is poor (*e. g.*, the famous Koch "cancer cure" is hidden behind the misprint "Kich"). The style throughout is hortatory and condemnatory; but probably the subject-matter does not permit the author to gloss over the minor frailties of the better pharmaceutical houses, or to intimate that at times a little quackery may even serve a useful therapeutic purpose. Altogether, the book makes interesting reading even for a physician. The sermon might have been better had it been briefer. J. C.

ATLAS OF HEMATOLOGY. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Head of Experimental Medicine, University of Oregon Medical School, Portland, and CLARICE M. ASHWORTH, Medical Illustrator, University of Oregon Medical School, Portland. Pp. 255; 325 illustrations and frontispiece, all in full color. San Francisco: J. W. Stacey, Inc., 1937. Price, $10.00.

AN Atlas of Hematology with none but colored illustrations is a rare product in this country where the cost of engravings in color seems so inordinately high. With this in mind, the cost of this volume is not excessive, especially in view of its general excellence. The drawings were obviously well and carefully done and the reproduction, by the Hicks Chatten Company of Portland, Oregon, unusually good. Nevertheless, the result is not quite up to that of Strumia's loose leaves of Hematological Tables (privately printed by the Bryn Mawr Hospital), the illustrations of which were done in Italy. Though less expensive, this latter work is much less extensive in scope.

Not intended to replace a textbook of hematology, Osgood's Atlas, with its 12 pages of General Principles of Hematologic Diagnosis, full legends to the illustrations, 7 chapters on the various hematologic conditions, an appendix on Methods, and a copious bibliography, should succeed in its aim of showing the physician how to make a systematic study of the blood in disease as a prerequisite of accurate diagnosis and proper therapy. The senior author, who has himself made excellent contributions to hematology, has given a sound picture, both in text and illustration, of hematology as understood by most Americans today. The magnification (2500 ×) is rather large for the eye accustomed to half that amount, but does permit reproduction of minute cellular detail. The use of Wright's stain, and numbering the cells in sequence both aid the physician and the prospective author in the positive identification of difficult cells. E. K.

DISORDERS OF THE BLOOD. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, G.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, the Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (New Zealand), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital; Late Assistant Pathologist, Christchurch Hospital, New Zealand. Pp. 582; 60 illustrations, 12 plates (8 colored) and 15 tables. Second Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937, Price, $7.50, with washable cloth cover.

OUR objections to Whitby and Britton's book are that it is seldom to be found when looked for on our library shelves and that it is wearing out (legitimately) from overuse. For such reasons, therefore, as well as on account of the notable advances in hematology in the two years that have elapsed since the appearance of the first edition in 1935, a new edition is welcome. The 35 extra pages of this edition are evenly distributed through the same chapter system as in the first edition—the greatest increase being 5 pages in the chapter on Technique. The approval expressed in the review of the first edition (*Am. J. Med. Sci.*, **191**, 279, 1936) can be repeated even more emphatically for the present one. E. K.

CHIRURGISCHE INDIKATIONEN. By RUDOLF NISSEN, O. Prof. D. Chirurgie, Direktor der 1. Chirurgischen Klinik der Universität Istanbul. Pp. 177. Leyden: A. W. Sijthoff's Uitgeversmaatschappij, N.V., 1937. Price, Paper, Hfl. 3.50; Bound, Hfl. 4.50.

THE results of surgery are in a large measure dependent on the general practitioner's knowledge of the proper and timely indications for operation. The author discusses a number of especially important and common problems in this field, including, on the one hand, emphasis on conditions demanding urgent operative intervention, and, on the other, the delineation of surgical indications in diseases in the borderline zone between internal medicine and surgery. There are chapters on injuries of skull and brain, diseases of the thoracic organs, diseases of the abdominal organs and colon, diseases of kidneys and ureters, goiter, tumors of the breast, injuries of the extremities, pyogenic infections, and tuberculosis of bones and joints. The presentation is concise, clear-cut and well balanced. The book will be found useful and instructive to those physicians with a command of German. R. K.

MATERNITY AND POST-OPERATIVE EXERCISES. (Twenty-one Exercises.) In Diagrams and Words, by MARGARET MORRIS, C.S.M.M.G., in collaboration with M. RANDELL, S.R.N., S.C.M., T.M.M.G. Introduction to Maternity Exercises by PROF. R. W. JOHNSTONE, C.B.E., M.D., F.R.C.S.E., F.C.O.G. Introduction to Post-operative Exercises by PROF. JOHN FRASER, M.C., M.D., F.R.C.S.E. Pp. 152; illustrated. New York: Oxford University Press, 1936. Price, $2.00.

THE preface and introductions are very adequate and should be most helpful in aiding the masseuse or teacher for the exercises to follow. Careful instructions and good diagrams used to explain all the exercises. Her excellent choice of exercises, particularly the emphasis on breathing and correct posture, helps to make this the most practical book of its kind.

M. R.

ROSE AND CARLESS MANUAL OF SURGERY. American (Fifteenth) Edition. Edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Fifteenth English Edition by CECIL P. G. WAKELEY, D.Sc. (LOND.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Senior Surgeon, King's College Hospital, etc. and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital, etc., Pp. 1586; 900 illustrations and 26 plates (18 in color). Baltimore: William Wood & Co., 1937. Price, $9.00.

IN this American edition, edited by Professor Coughlin, there have been omitted certain specialties from sections of the British edition which are not considered within the scope of the general surgeon in this country. The dedicatory page contains an illustration of the bust of Lord Lister now in the Royal College of Surgeons of England, together with the original authors' dedication which appeared in the first edition in 1898.

The volume has been extensively rearranged and in parts largely rewritten, with some increase of the size of the book (43 pages). As the index was not specially prepared for the American edition, numerous entries in the index cannot be found in the text.

The material dealing with surgical diagnosis and the maneuvers of surgical treatment is extensively presented. On the other hand the historical aspects of surgery are only occasionally referred to and the preoperative and postoperative care is very frequently inadequately discussed. The section on anesthesia is often not in accord with the best traditions of American anesthetists. Nitrous oxide is not "undoubtedly our safest anesthetic" even when combined with oxygen. The section on spinal anesthesia extensively discusses the use of stovaine. One of the major defects of the volume is the failure to incorporate in the discussions of various diseases the disturbances in function from a physiological viewpoint. While the Reviewer feels that the volume will provide a ready reference for a single volume manual for surgical practitioners, he believes that it will not take the place of certain of the shorter volumes that have recently been presented for use in courses given undergraduate students.

I. R.

THE THYROID AND ITS DISEASES. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital. Being an Account based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital by 14 physicians and surgeons, and many other collaborators, Past and Present. Pp. 602; 73 illustrations. Philadelphia: J. B. Lippincott Company, 1937. Price, $6.00.

THIS is an exceedingly valuable and important book, representing, as it does, the clinical experience and investigative work of over 20 years in the Thyroid Clinic of the Massachusetts General Hospital. Beginning with a description of the anatomy, physiology and biochemistry of the normal gland, there are then covered the various diseases of the thyroid. Two chapters deal with thyroid administration and total thyroidectomy, respectively, in diseases of other than thyroid origin. While disclaiming an encyclopedic scope for the volume, the author nevertheless fully covers the subject from the practical standpoint with an adequate discussion of the literature and a fair presentation of controversial points. The book is written in a clear, interesting, chatty style that makes it pleasant reading. This text is warmly recommended to all practitioners, internists and students.

R. K.

PRACTICAL TALKS ON KIDNEY DISEASE. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia. Pp. 176; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, $3.00.

THIS small volume deals with the practical aspects of the diagnosis and treatment of glomerulonephritis, nephrosis and nephrosclerosis. An attempt is made to review briefly the essential facts of renal physiology, tests of renal function and water balance. The material, set forth in easily readable style, consists of the accepted views on these subjects. The scope of the book is by intent such that it lacks the value of a reference work, and since it contains little of practical value which cannot be found in standard textbooks, is chiefly useful as a convenient compilation of standard information in this field. K. E.

THE KINESIOLOGY OF CORRECTIVE EXERCISE. By GERTRUDE HAWLEY, M.A., Assistant Director, Women's Gymnasium, Stanford University, Calif. Pp. 268; 107 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $2.75.

AN extremely thorough test with an excellent selection of exercises. The author's explanation of the kinesiology of these movements is clear and well defined, and should be most helpful to any teacher of therapeutic gymnastics. This book not only deals with faulty body mechanics, but also teaches the proper use of the body, which few people understand and which is the fundamental reason for poor posture. It will be a valuable addition to any professional library. M. R.

NEW BOOKS.

The Management of the Pneumonias. For Physicians and Medical Students. By JESSE G. M. BULLOWA, B.A., M.D., Clinical Professor of Medicine, New York University College of Medicine; Visiting Physician and Director of Littauer Pneumonia Research Fund, Harlem Hospital; Visiting Physician, Willard Parker Hospital. Pp. 508; 142 illustrations. New York: Oxford University Press, 1937. Price, $8.50.

Functional Activities of Pancreas and Liver. A Study of Objective Methods for the Estimation of Function Levels in Health or Disease. By CHARLES W. MCCLURE, M.D., Gastroenterologist to Fifth Medical Service, Boston City Hospital; Assistant Professor of Gastroenterology, Boston University School of Medicine. Special chapters by TAGE CHRISTIANSEN, M.D., Resident Physician, Medical Department, County Hospital of Copenhagen, Denmark, and the late ALLAN W. ROWE, PH.D., formerly Director of Research, Evans Memorial, Boston, Mass. With a Foreword by SAMUEL WEISS, M.D., F.A.C.P., New York. Pp. 318; 66 illustrations. New York: Medical Authors' Publishing Company, 1937. (Price not given.)

Maternal Deaths—The Ways to Prevention. By IAGO GALDSTON, M.D., Secretary, Medical Information Bureau of the New York Academy of Medicine. Pp. 115. New York: The Commonwealth Fund, 1937. Price, Paper bound, 50c; Cloth bound, 75c.

Manual of Human Dissection. By EDWIN M. SHEARER, PH.D., Associate Professor of Anatomy, New York University College of Medicine. Pp. 321; 79 illustrations (author's original drawings). Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.25.

Eyestrain and Convergence. By N. A. STUTTERHEIM, M.D. (RAND), ARTS STAATS-EXAMEN, HOLLAND), part-time Ophthalmic Surgeon to the Johannesburg School Clinic, Transvaal Education Department; late Assistant to Eye Clinic, University, Leyden. Pp. 89; 2 illustrations. London: H. K. Lewis & Co., Ltd., 1937. Price, 7s. 6d.

Abstracts. Proceedings of Meetings of the New York Pathological Society, held Nov. 26, 1935; Dec. 26, 1935; Jan. 23, 1936; Feb. 18, 1936; Mar. 26, 1936; Apr. 23, 1936; May 28, 1936. Reprinted from the *Archives of Pathology.* Pp. 42.

The Collapse Therapy of Pulmonary Tuberculosis. By JOHN ALEXANDER, B.S., M.A., M.D., F.A.C.S., Professor of Surgery, University of Michigan; Surgeon-in-Charge, Division of Thoracic Surgery, Department of Surgery, University of Michigan Hospital. With contributions of Chapters III and IV on Physiological Principles and Pathology of Pulmonary Collapse by MAX PINNER, M.D., F.A.C.P., Herman M. Biggs Memorial Hospital, Ithaca, N. Y., etc.; Chapters XI and XII on Pneumothorax by JOHN BLAIR BARNWELL, B.A., M.D., Associate Professor of Internal Medicine, University of Michigan, etc.; Chapter XV on Oleothorax by KIRBY SMITH HOWLETT, JR., M.S., M.D., Resident, Laurel Hills State Tuberculosis Sanatorium, Shelton, Conn. Pp. 705; 367 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $15.00.

Socialized Medicine in the Soviet Union. By HENRY E. SIGERIST, M.D., WILLIAM H. WELCH, Professor of the History of Medicine, The Johns Hopkins University. Pp. 378; illustrated. New York: W. W. Norton & Co., Inc., 1937. Price, $3.50.

Physiological Chemistry of the Bile. By HARRY SOBOTKA, Chemist to The Mount Sinai Hospital, New York. Pp. 202; 4 illustrations. Baltimore: The Williams & Wilkins Company, 1937. Price, $3.00.

Archiv für Kresilaufforschung. Beihefte zur "Zeitschrift für Kreislaufforschung." Band 1, Heft 1–6 (July, 1937); 7–8 (Oktober, 1937). Herausgegeben VON DR. EB. KOCH, Professor für Physiologie, Kerckhoff-Herzforschungs Institut, Bad Nauheim, and DR. ED. STADLER, Professor Leitender Arzt am Stadtkrankenhaus, Plauen i. V. Pp. Heft 1–6, 224; Heft 7–8, 80; each illustrated. Dresden: Theodor Steinkopff, 1937. (No price given.)

Die Störungen der Sexualfunktion bei Mann und Weib. By DR. LUDWIG CHIAVACCI, Wien. Pp. 146. Wien: Franz Deuticke, 1938. Price, Paper, M. 4.60; Bound, M. 5.40.

The Diagnosis and Treatment of Sexual Disorders in the Male and Female, Including Sterility and Impotence. By MAX HUHNER, M.D., formerly Chief of Clinic, Genitourinary Department, Mount Sinai Hospital Dispensary; Attending Genitourinary Surgeon, Bellevue Hospital, etc. Pp. 490; illustrated. Philadelphia: F. A. Davis Company, 1937. Price, $5.00.

Twenty-five Years of Health Progress. A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company, 1911 to 1935. By LOUIS I. DUBLIN, PH.D., Third Vice-President and Statistician, and ALFRED J. LOTKA, D.Sc., Assistant Statistician. With the collaboration of the staff of the Statistical Bureau. Pp. 611; many charts and tables. New York: Metropolitan Life Insurance Company, 1937. (No price given.)

A Pediatrician in Search of Mental Hygiene. By BRONSON CROTHERS, M.D., Assistant Professor of Pediatrics, Harvard Medical School; Visiting Physician to the Children's Hospital and to The Infants' Hospital, Boston. Pp. 271. New York: The Commonwealth Fund, 1937. Price, $2.00.

Appendicitis. A Clinical Study. By W. H. Bowen, Hon. M.A. (Camb.), M.S. (Lond.), F.R.C.S., Hon. Surgeon to Addenbrooke's Hospital, Cambridge; Hon. Consulting Surgeon to Royston County Hospital; Examiner in Surgery, University of Cambridge, etc. Pp. 202. Cambridge: The University Press, 1937. Price, $2.50.

Phenomenon of Local Tissue Reactivity and its Immunological, Pathological and Clinical Significance. By Gregory Shwartzman, M.D., Bacteriologist, Mount Sinai Hospital, New York. Foreword by Jules Bordet, M.D., Paris. Pp. 461; 67 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1937. Price, $7.50.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. X. Tagung zu Bad Nauheim vom 13.–14. März, 1937. Hauptthema: Kreislauf und Innere Sekretion. Herausgegeben von Prof. Dr. Eb. Koch, Bad Nauheim. Pp. 320; 140 illustrations. Dresden: Verlag von Theodor Steinkopff, 1937. Price, Rm. 15.

The Cerebrospinal Fluid. By H. Houston Merritt, M.D., Assistant Professor of Neurology, Harvard Medical School; Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital, and Frank Fremont-Smith, M.D., formerly Assistant Professor of Neuropathology, Harvard Medical School; formerly Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital. With a Foreword by James B. Ayer, M.D. Pp. 333; illustrated. Philadelphia: W. B. Saunders Company, 1937. Price, $5.00.

NEW EDITIONS.

Practical Physiological Chemistry. By Philip B. Hawk, M.S., Ph.D., President of the Food Research Laboratories, Inc., New York City, and Olaf Bergeim, M. S., Ph.D., Associate Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. In collaboration with Bernard L. Oser, Ph.D., Director of the Food Research Laboratories, Inc., New York City, and Arthur G. Cole, Ph.D., Assistant Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. Pp. 968; 281 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $8.00.

A Diabetic Manual for the Mutual Use of Doctor and Patient. By Elliott P. Joslin, M.D., Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital, Boston. Pp. 219; 49 illustrations and 1 colored plate. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $2.00.

Methods of Treatment. By Logan Clendening, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals; Consulting Physician, Kansas City General Hospital; Physician to St. Luke's Hospital, Kansas City, Mo. With chapters on special subjects by H. C. Andersson, M.D.; Ursulla Brunner, R.N.; J. B. Cowherd, M.D.; Paul Gempel, M.D.; H. P. Kuhn, M.D.; Carl O. Rickter, M.G.; F. C. Neff, M.D.; E. H. Skinner, M.D.; E. R. DeWeese, M.D.; and O. R. Withers, M.D. Pp. 879; 103 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1937. Price, $10.00.

"This book was planned to furnish an outline of all the methods of treatment in internal medicine. Its design contemplates gathering together material otherwise widely scattered in medical literature; as, for instance, descriptions of the technic of spinal puncture, blood transfusion, the wet pack, and the ketogenic diet. In the sections on treatment in texts on the practice of medicine a method is recommended usually without any instructions as to technic, usually, indeed, without any discussion of the rationale behind it." (From author's Preface.)

A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners. By OLIVER S. ORMSBY, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago; Dermatologist to the Presbyterian and Saint Anthony's Hospitals and the Home for Destitute Crippled Children, etc. With revision of the Histopathology and Mycology by CLARK WYLIE FINNERUD, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1334; 658 illustrations and 3 colored plates. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $12.00.

Crippled Children. Their Treatment and Orthopedic Nursing. By EARL D. MCBRIDE, B.S., M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, University of Oklahoma, School of Medicine; Attending Orthopedic Surgeon to St. Anthony Hospital, etc., in collaboration with WINIFRED R. SINK, A.B., R.N., Educational Director, Grace Hospital School of Nursing, Detroit; formerly Head Nurse of James Whitcomb Riley Hospital of the Indiana University Group. Pp. 379; 195 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1937. Price, $3.50.

The second edition is an improvement upon the first, due in large part to the collaboration of a nurse eminent in the field of teaching. It is now possible to recommend this book for the use of nurses specializing in the care of crippled children.

The Micromotist's Vade-Mecum (Bolles Lee). A Handbook of the Methods of Animal and Plant Microscopic Anatomy. Edited by J. BRONTË GATENBY, M.A., PH.D. (DUBL.), B.A., B.SC., D.PHIL. (OXON.), D.SC. (LOND.), Professor of Zoölogy and Comparative Anatomy, Trinity College, Dublin, and THEOPHILUS S. PAINTER, A.B. (ROANOKE), A.M., PH.D. (YALE), Professor of Zoölogy, Texas University, with 10 collaborators. Pp. 784; 11 illustrations. Tenth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $9.00.

Manual of Clinical and Laboratory Technic. By HIRAM B. WEISS, A.B., M.D., F.A.C.P., Associate Professor of Medicine, College of Medicine, University of Cincinnati, Cincinnati, and RAPHAEL ISAACS, A.M., M.D., F.A.C.P., Associate Professor of Medicine; Assistant Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor. Pp. 141. Fifth edition, reset. Philadelphia: W. B. Saunders Company, 1937. Price, $1.50.

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PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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RECENT CONCEPTS IN THE PATHOGENESIS OF DIASTOLIC HYPERTENSION.

It was the work of Allbutt 40 years ago which led to the classification of diastolic hypertension into 2 main groups: (1) Essential, or primary hypertension, also termed hyperpiesia; and (2) secondary hypertension, resulting from some known disease and most frequently occurring upon the basis of a renal lesion, adrenal tumor, or coarctation of the aorta. Much work has been done recently to throw light upon the pathogenesis of both of these types

Heredity. Essential hypertension is peculiar to man. Although much work has been done on its hereditary aspects, there remains much confusion in the evaluation of this factor. Such a disease as this, not dependent upon a malformation or congenital defect at birth, in which the tissues show no structural change until, or even after, the disease has developed, is often extremely difficult to evaluate genetically. Before the development of the disease, these tissues look no different from those of other individuals, yet the predisposition for the development of the disease is there. The length of time from birth to the development of the clinical picture, usually over 40 years, has been an important factor in clouding the recognition of heredity in essential hypertension. The patient may die before this time of other causes. There are many other reasons why the human does not lend himself well to the study of genetics.[72] Human matings lack the control attending the study of experimental animals; the life span is too long for one observer to study many generations; family data are notoriously inadequate, and families are not large; environmental factors are often necessary as precipitating causes. The physician himself may be a factor. He not only often lacks interest in these aspects of disease but through inadequacies in diagnosis and the confusion of primary and secondary hypertension he may invalidate the results. Absence of hypertension because of examination before it develops leads to inadequate data. Recessiveness coupled with the lack of control of matings and the long life span of man produce an irregular occurrence of disease that is difficult to trace familially. The very frequency of disease may be a disadvantage in a genetic study. As Allan[2] pointed out, hypertension may be present in up to 40% of the population above the age of 60. Such figures make it possible that any individual may have some member of the family with hypertension.

Methods[72] most fruitful in the establishment of heredity as a basic factor in essential hypertension, as well as in other hereditary diseases, include the incidence of consanguineous marriage in parents. This is about 0.2% in the general population. Figures above this indicate hereditary factors and recessiveness of the factor. Studies of identical twins are obviously helpful. The frequency of disease in related and unrelated persons, the study of pedigrees, and statistical analyses are particularly enlightening. All of these methods have been applied to hypertension. An enumeration of all such data would require an appalling amount of time. Carefully controlled studies indicate that, in patients with essential hypertension, the familial incidence of vascular disease far exceeds that of patients suffering from other complaints. Family after family is reported with definite hereditary trends.[46,c] Ayman made a direct study of the blood pressure in 1524 persons in 277 families. A tendency toward elevated blood pressure early in life was found in hypertensive families, a finding which was largely absent in members of normal families. Palmer and Thorp[51] have found the incidence of a family history of degenerative vascular disease definitely greater in cases of hypertension graded as moderate or severe. They interpreted this finding as representing constitutional susceptibility more regularly present in these cases. Weitz[71] tried to circumvent the difficulties of following many generations through the often inaccurate histories of the patient by studying the collateral family groups. These individuals were living and could be submitted to examination. Thus, "objective signs of disease were substituted for hearsay evidence in the history." Asymptomatic cases were available as well. Omitting the details of his analysis, his conclusions, that the predisposition to essential hypertension behaves in the majority of cases as a Mendelian dominant, might be quoted here. Ayman[4a] has described a personality type, both emotionally and physically hyperactive, not only in the patient with established hypertension, but also in certain of their children with mildly elevated blood-pressure readings. These findings he interprets to indicate the hereditary nature of the personality as well as of the blood pressure.

Studies of identical twins subjected to the opposing strains of widely divergent environmental factors confirm the above conclusions.[72] Vascular reactions may be so similar in identical twins that capillary microscopy may be used as a means of establishing the diagnosis of their relationship.

There are, of course, those who deny heredity as a factor of importance in essential hypertension. Janeway considered it as of minor importance. Advocates of this view assign an important rôle to environment, particularly in its relationship to psychic reactions. It is often pointed out that the negro in his native land seldom develops hypertension. Donnison[19] and many others have observed many negroes in Africa and agree on the extreme rarity of hypertension. However, in this country, the negro is commonly afflicted with hypertension. Schulze and Schwab[64] found an incidence of hypertension in the American negro $2\frac{1}{2}$ times greater than that of the white American. An admixture of white blood is perhaps the rule in the American negro, a fact which introduces complicating genetic factors. Schulze and Schwab state that evidence of admixture with the white race in their patients was negligible and insufficient to reconcile the disparity in the incidence of essential hypertension in the African and American negroes. The frequency of hypertension in the negro would require the assumption that all were hybrids, and, since the incidence of hypertension is greater in the negro than in the white, "it would be necessary to infringe on the Mendelian law to explain the higher incidence of a character in the hybrid than in the parent carrying the character."

Racial differences in the incidence of essential hypertension are not confined to the negro. The Chinese, for example, are little afflicted by hypertension. Wang,[67] in 10,310 admissions to Hsiang Ya Hospital from 1932 to 1935, found only 58 instances of essential hypertension, 34 in males and 24 in females. Others[22,66] have shown that the blood pressure of Chinese is lower, in general, than that of Occidentals. However, doubt as to the hereditary importance of these differences is shown by the fact that foreigners tend to develop a lower blood pressure after a stay in China, which disappears, with return to the previous level, when they return home. Environmental factors—mode of life, diet, climate—may be responsible but have not been evaluated. Superficially, environment appears to be the primary causative agent, but one must remember that all negroes do not develop hypertension and that the possibility exists that the environment may apply a precipitating cause or causes for hypertension in those who have inherited a predisposition but have had no precipitating factor in their home environment.

Hines[35] has studied the hereditary aspects from an entirely new approach. He applied the reaction of the blood pressure to a standard stimulus (cold pressor test) in members of hypertensive and nonhypertensive families, including 10 pairs of twins. He found a positive family history of hypertensive cardiovascular disease 5 times as frequently among individuals who had hypertension or who were hyperreactors than among those who reacted normally to the test. He has not found any hyperreactor who did not have one parent with hypertension, or who was a hyperreactor, indicating the probability that the trait is inherited as a dominant characteristic.

The final evaluation of heredity in essential hypertension remains for the future.

The Nature of Increased Peripheral Resistance in Diastolic Hypertension. It is well known that an elevation in diastolic blood pressure to 100 mm. of mercury or more can be brought about by at least 1 of 4 mechanisms—increased blood viscosity, increased blood volume, increased cardiac output, or an increase in peripheral resistance. Observations[9,70] indicate that in chronic hypertension, viscosity, blood volume and cardiac output do not differ significantly from normal, but that a distinct and marked increase in peripheral resistance, especially in the arterioles,[20] is an invariable finding.

The control of peripheral resistance (arteriolar tone) in diastolic hypertension could be moderated through at least 3 mechanisms: nervous control, a local change, or hormonal or chemical substances. Studies in the nature of the peripheral resistance have been largely controversial until the recent work of Prinzmetal and Wilson[55] in this country and of Pickering[54a] in England.

The Question of Nervous Control. Prinzmetal and Wilson attacked the problem by the use of an apparatus to measure blood flow through the extremity. They first investigated the widespread theory that increased peripheral resistance in the splanchnic area alone was responsible for elevated arterial tension. If this were so, the normal cardiac output should produce a greater blood flow through the periphery in the hypertensive individual than in the normal person. No change in blood flow from the normal was noted in malignant, benign, and secondary hypertension, implying that the increased vascular resistance in hypertension is no greater in the splanchnic area than in the arm. The peripheral resistance is, therefore, generally elevated. This is in keeping with the histologic changes in the arterioles of voluntary muscle.[41]

Using the same technique, together with the application of heat and reactive hyperemia, these same authors were able to show that the vessels of hypertensive individuals were capable of dilatation and that the increased peripheral resistance is due to a generalized vascular hypertonus and not to primary changes in the blood-vessels.

Having established the presence of generalized vascular spasm, these observers were concerned with the possible mechanisms of its production, as stated above. Three possibilities were obvious, nervous control through the vasomotor nerves, a local fault, or a chemical or hormonal influence. Their approach was directly upon the nervous theory because of the known influences of the vasomotor nerves on the diameter of arterioles and the level of the blood pressure. They reasoned that if the peripheral resistance in hypertension were dependent upon vasomotor stimulation one could assume that any procedure which would release vasomotor tone in a part would produce a greater blood flow through that part in hypertensives than in normal individuals. Using the same blood-flow technique, they produced vasomotor release by both heat and novocaine injection of nerves. Increases in blood flow under these circumstances were essentially the same in patients with benign, malignant, or secondary hypertension and in normal individuals. The results, then, failed to support the hypothesis of exaggerated vasomotor tone as the cause of hypertension.

Pickering,[54a] working in England independently from Prinzmetal and Wilson, but using similar methods, reached similar conclusions. However, in the determination of the influence of the vasomotor nerves he used a calorimetric method to determine blood flow. The use of the latter technique is all the more important in that it confirms the results of the plethysmographic method that hypertension is not nervous in origin. Their results in coarctation of the aorta differ. This will be discussed later.

In essential hypertension, the results of these investigations indicate "that normal vasomotor activity is superimposed on an intrinsic vascular hypertonus which is independent of the vasomotor nerves."

Vasomotor responses may affect the level of the blood pressure to a marked degree but that does "not prove that the hypertonus of arterial hypertension is vasomotor in origin." Pickering states that, as the Hines-Brown test shows,[36] the vasomotor nerves remain active in hypertension. There is "little doubt that vasoconstriction of nervous origin does constitute a considerable fraction of the peripheral resistance in persistent hypertension," as in normal individuals. But he contends further, from the above results, that it does not constitute the abnormal factor responsible for raised arterial pressure. He and Kissen were unable to confirm the Hines-Brown test. They obtained variable results, especially in their elderly control series and in patients with essential hypertension. The average size of the response was approximately the same in elderly subjects with normal blood pressure as in those suffering from essential hypertension.

As convincing as the above evidence appears in establishing the fundamental nature of essential hypertension, it is not as yet fully accepted. Page and Heuer[48b] conclude that it "seems impossible on the basis of contemporary evidence to decide whether hypertonus of vessels in hypertension is of nervous origin." To be sure, the mass of evidence in the literature lends credence to the nervous theory. However, as far as this Reviewer has been able to determine, it is entirely equivocal. Prinzmetal and Wilson, in their search of the literature, also failed to find conclusive evidence to support the hypothesis of exaggerated vasoconstrictor tone. The marked drop in blood pressure attending spinal anesthesia and anterior root or splanchnic nerve section is, of course, compatible with the neurogenic theory and does indicate the profound influence of the nervous system on the arterioles, but in no wise proves the rôle of the nervous system as the fundamental cause of essential hypertension. The association of nervous and mental instability, and the relationship of the occurrence of essential hypertension to our complicated civilization are no more convincing. Although the evidence for non-nervous origin of essential hypertension is meager, it is clearcut, to the point, and convincing.

Pickering[54c] studied the transient hypertension of acute nephritis. Circulation time was the same during and after the hypertension so that increased cardiac output as a cause of hypertension was not likely. By applying the blood-flow method he showed that some, and probably most, cases of this type of transient hypertension are due to vasoconstriction of vasomotor nervous origin. He reasoned that this vasoconstriction might arise in one of two ways—by a centrally acting pressor substance or by a reflex mechanism. According to these results the acute hypertension of nephritis differs in its pathogenesis from the chronic type of renal origin. Results in experimental oxalate nephritis[3] support such a mechanism. In the rabbit, hypertension so produced is abolished by renal denervation.

The evaluation of the nervous factor in hypertensive states is exceedingly important in that it has a direct bearing upon treatment. The present highly developed state of neurosurgical technique as applied to peripheral vascular disease has naturally led to a consideration of similar methods in the treatment of hypertension. Although a consideration of such methods and results does not constitute a part of this review, the relationship of such methods to the pathogenesis of hypertension will be briefly summarized.

Vasomotor tone has a direct influence on the tonic state of the arterioles and, in turn, on the blood pressure. It is upon this nervous basis, particularly vasoconstriction in the splanchnic area, that splanchnic section has been proposed. If one accepts the work of Prinzmetal and Wilson and that of Pickering, any surgical approach to the treatment of diastolic hypertension based on abnormal vasomotor tone as the cause of the vasoconstriction appears irrational. "Even in such a case vasomotor release following operation would, by release of normal vasoconstrictor tone, produce some fall in blood pressure but would not affect the spasm responsible for the hypertension."[58] Yet if splanchnic section caused no injury to the patient and if the accompanying fall in blood pressure were accompanied by a sufficient blood supply to the essential organs, the release from cardiac and vascular strain, if it persisted, would no doubt prove beneficial. The work of Page[47a] indicates that considerable reduction in arterial tension, if not sudden, may take place without a change in the urea clearance. One would assume, therefore, that renal function is not affected. Another objection, as Page and Heuer[48b] have pointed out, is that sympathectomy in a limited area would lead one to expect vasodilatation in that area and continued constriction in the remainder of the body with impaired blood flow. They have found, however, that vessels relax in areas other than those subjected to denervation, for example in the eyegrounds. Such changes, even though not directed at the primary factor producing the disease, would prove beneficial if the reduction were maintained. Despite this observation, Weiss[68] feels that the decrease in vasomotor tone in one region of the body may produce a suboptimal blood flow in other organs, where a more constricted state of the arterioles exists along with a diminished blood pressure. The eventual outcome of such a change would be deleterious and late in its appearance.

Experimentally in dogs removal of the complete sympathetic chain[32] has been followed by restoration of blood pressure to normal in 94 to 225 days, at which time cardiac output, blood viscosity, and blood volume are unchanged, indicating a compensation by some other vasoconstrictor mechanism. The same phenomenon occurs in the human being with splanchnic section. Page and Heuer[34,48b] performed this operation with removal of the lower thoracic sympathetic ganglia in 6 patients with essential and 3 with malignant hypertension. Blood pressure was diminished in each instance for some months only to rise again to the pre-operative level, and for periods ranging from 6 months to 1 year either had continued at this level or became more elevated. Results, therefore, were disappointing. The same authors[48c] have used anterior root section with better results. This procedure depresses the blood pressure by the same mechanism, that is, splanchnic dilatation. In 17 patients with either the benign or malignant types of hypertension, 6 months after operation it was found that the benign group had reacted well, the malignant group had not. Brown, who with Adson proposed this operation, believes it useless in malignant hypertension, but also observed good results, up to 5 years postoperative, in the benign variety.[8] Such results indicate that nerve section will at least remove the vasomotor effect in the benign group, if not far advanced, sufficiently to effect a significant drop in blood pressure for many months. Its ultimate value in the treatment of hypertension, the authors agree, has not yet been established.

Splanchnic section has also been done to reduce adrenal secretion, to diminish peripheral blood volume and to abolish abnormal vasoconstrictor effects of renal origin. At least 15% of over 100 patients in one series have gone over 6 months with normal blood pressure.[53] Data to be given later indicate that epinephrine is not excreted in excess in hypertension except in a few cases of paroxysmal type associated with chromaffin tumors, and the operation in essential hypertension appears to have no foundation upon this basis.

Renal denervation has also been done in patients both with essential hypertension and with chronic nephritis.[48a] The procedure had no immediate effect upon renal efficiency as measured by the urea clearance test. The fall in blood pressure lasted for weeks to months but was not permanent.

The advice of Weiss[68] in considering the use of such procedures is sound. He states "Physicians should accept therapeutic claims and particularly new surgical procedures only after proper evaluation of the problem, and when there is strong supporting evidence. In case of arterial hypertension the presentation of such therapeutic proof is at best difficult. For the present, therefore, it seems advisable to leave the surgical treatment of arterial hypertension in the hands of those surgeons who believe that they can answer the problems raised in this discussion and who can eventually present adequate proof that there is lasting benefit to their patients."

There have been a number of attempts, particularly in Europe, to show a relationship between the carotid sinus mechanism and persistent hypertension. The carotid sinus consists of a small bulging at the junction of the common and internal carotid arteries. Nervous impulses from its walls are conducted away through the carotid sinus nerve and eventuate in cardiac slowing and vasodilatation. Elevated pressure in the carotid sinus produces a fall in cardiac rate and general arterial tension. Decreased pressure produces the reverse. That this depressor effect is active is evidenced by the observations of Bronk and Stella[7] that a rhythmic discharge of nervous impulses took place over the carotid sinus nerve with adequate pressure in the sinus (40 mm. of mercury in the rabbit). The rate of discharge was also proportional to the pressure. If the carotid sinus nerve were cut one would expect a rise in blood pressure; and that is exactly what Bucy[10] found. In section of the glossopharyngeal nerve for neuralgia, the carotid sinus fibers are sectioned. Bucy noted a marked rise in blood pressure postoperatively with a return to normal in 2 weeks. The rise was not due to increased intracranial pressure for the spinal fluid pressure was normal. Section of both nerves and the aortic depressor nerves in animals has produced similar results but the blood pressure has not returned entirely to normal, so that persistent hypertension resulted. Such a rise is evident only when the animal is awake and more or less excited, and disappears when it is asleep or quiet.[56]

Such observations as the above have led a number of investigators to consider the carotid sinus mechanism in human hypertension.[39] Continental observers (Mies) have demonstrated marked changes in blood pressure and cardiac rate by pressure on the carotid sinus, but no rise in blood pressure by obliteration of the arteries below the sinus, indicating a possibility that the elevated blood pressure may have resulted from a disturbance in the carotid sinus mechanism characterized by slight or no response to the stimulus of arterial pressure within the sinus. These observations prompted Pickering, Kissen and Rothschild[56] to investigate the carotid sinus mechanism in hypertension. Starting with the previous observations that in normals the fall in pulse and respiratory rates with carotid sinus compression depends on the initial value of these rates, these authors found that a fall in blood pressure in either normal or elevated arterial tension, after histamine, was approximately proportional to the initial blood pressure. The percentage fall in blood pressure corresponded fairly closely to the fall in heart rate. A second factor was the degree of sclerosis of the carotid arteries. The work of others was confirmed in that the percentage fall of blood pressure and pulse rate reflected fairly accurately the extent of sclerosis in the larger arteries and the differences in response in the groups studied were attributed to differences in the initial levels and presence or absence of sclerosis. These results differed completely from those of continental observers. Pickering is convinced that hypertension in the human and experimental hypertension of carotid sinus denervation are different, although he does not deny that there may be examples in man similar to the experimental form. Absence of tachycardia, however, cannot be used as an argument against the occurrence of this type of hypertension in man for in 2 of Bucy's cases no significant changes in pulse rate were observed following nerve section. Weiss[69] describes, in his types of response to carotid sinus pressure, a primary reflex vasodilatation entirely unrelated to cardiac slowing or any form of cardiac arrhythmia.

The blood-flow method of investigation of the nature of the peripheral resistance in diastolic hypertension has been applied[54a,58] to coarctation of the aorta as well. Results are conflicting. Prinzmetal and Wilson found, in coarctation of the aorta with hypertension in the upper and hypotension in the lower extremities, that vasomotor release produced a greater increase in flow in the arm than in the arm of normal controls or patients with generalized hypertension, indicating that the increased vascular hypertonus of the upper extremities in this disease is vasomotor in origin, unlike that of benign, malignant, and secondary hypertension. Such constriction they "regarded as a compensatory mechanism which maintains the normal distribution of blood throughout the body." Pickering's results were similar to those in other types of hypertension, and since a circulating chemical or pressor factor alone cannot account for hypertension in one portion of the body and normal blood pressure in another, he considered the defect in coarctation a local fault. The divergent results in this study demand further work for final conclusions. Histologic study[31] of the arterioles of muscle and skin from the arm and leg of such individuals has not been helpful.

The Question of Chemical or Hormonal Control. The possibility of a circulating chemical or hormone as the cause of the abnormal arteriolar constriction of diastolic hypertension is not new. Volhard had long championed such a theory. However, since the work demonstrating the non-nervous origin of this disease, interest in this mechanism has become more widespread. Volhard applied this theory first to "pale" hypertension and not "red" (essential) hypertension. Bohn[6] confirmed the presence of a pressor substance in the blood of the "pale" hypertensive, with negative results in the "red" variety, as well as in normal individuals. Aitken and Wilson[1] were unable to confirm the results of Bohn and ended in a criticism of his methods and results. Capps and his associates[12] agree with Aitken and Wilson.

Most of these experiments on circulating pressor substances have been carried out either by the introduction of extracts of the blood of affected individuals into animals and into animal preparations for physiologic tests for known pressor bodies, such as adrenalin and pituitrin, or by the transfusion to normal individuals or animals of the blood of hypertensive subjects. The results are confusing and often contradictory.

The work of Bohn, and of Aitken and Wilson, has just been mentioned. Danzer, Brody and Miles[17] injected the unchanged blood of patients with hypertension into cats with a resultant pressor effect. Curtis, Moncrieff and Wright[15] could not confirm this result. They used decerebrated cats with low blood pressure and arteriolar tone so that the vessels were more likely to be affected. Ten to 20 cc. of blood produced no effects greater than one would expect from an equal volume of any fluid.

Others[18,47b] have been equally unsuccessful in the demonstration of pressor substances. de Wesselow and Griffiths, using an alcoholic extract of whole blood and of plasma from patients with essential hypertension, malignant hypertension, chronic glomerular nephritis and pre-eclamptic toxemia, subjected to ultrafiltration, found the only suggestion of a pressor substance in blood from patients with essential hypertension, where Bohn found none. Even in this group some extracts gave curves like the normals and the authors did not feel justified in concluding that pressor bodies were present in the blood. Page found that extracts of human plasma and other body fluids contained substances with a pressor action when injected into test animals. Its extraction with alcohol, solubility in water and acetone, and extraction from water by chloroform suggested an organic base. Failure to appear in the ultrafiltrate suggested a combination with the plasma colloids. However, no evidence was produced that the amounts of this pressor substance were increased in the blood or body fluids of patients with essential or secondary hypertension. Pickering[54b] quotes a number of German references indicating the presence of pressor bodies in the blood, and, in one instance, the demonstration of a diminished value for a depressor substance in essential hypertension.

The possibility exists, when extracts of blood are used, that a pressor substance may either be destroyed or lost in its preparation or that such a substance may be formed by the process. This possibility is a real one, as shown by de Wesselow and Griffiths,[18] who demonstrated that adrenalin was readily ultrafiltered from saline, but if added to plasma and ultrafiltered, the ultrafiltrate was devoid of pressor activity. Pituitrin added to blood was recoverable in the alcoholic extracts, but in acid plasma of pH 4.5 the extract was destitute of pressor effect. This danger is circumvented by the transfusion of unchanged blood from hypertensive patients into non-hypertensive persons and noting the effects on the blood pressure. Results by this method have been uniformly negative. Høst tried the procedure in 1931.[37] Pickering[54b] injected 350 to 600 cc. of blood from hypertensives into non-hypertensive individuals on 7 occasions. His results suggested that the blood of patients with essential hypertension is similar to normal blood in its content of pressor and depressor substances, and oppose the idea of an excess of pressor substance, or deficit of depressor substance. However, they do not exclude the possibility that hypertension may be due to intervention of a chemical which is not circulating but is fixed in the tissues. Objection might be raised that the recipients were too ill to respond or that the pressor substance was rapidly destroyed before entering the recipient. The patients were not gravely ill and transfusion in less than 1 minute speaks against the latter of these arguments. A third objection that dilution of the donor's blood by the recipient might reduce the concentration below the threshold level for a pressor effect is justifiable and is answered most satisfactorily by the procedure of Prinzmetal, Friedman and Rosenthal[59] in which hypertensive patients were cross-transfused with individuals with normal cardiovascular trees. Blood volumes were not appreciably changed in either patient, and blood to the amounts of 500 to 2000 cc. was transfused. Congo red was injected into 1 subject before transfusion and 42% of the dye found in the blood of the recipient. No changes in blood pressure were noted in these patients, indicating that, even with a transference of large volumes of blood, minimizing the dilution factor, evidence of pressor or depressor principles was lacking.

Aside from the injection of blood extracts into animals and the transfusion of hypertensive blood into both animals and humans with normal blood pressure, various investigators have attempted to relate pressor substances to hypertension by physiologic tests for known and unknown pressor substances. For example, the denervated rabbit's ear[25,30] is known to be sensitive to pressor substances in high dilution such as epinephrine in dilutions of 1 to 100,000,000 and pitressin, 1 to 150,000. Perfusion of such preparations with whole, undiluted blood plasma has not given evidence favoring a direct, peripherally acting, circulating pressor substance.[25] Leiter[43] also concludes, from his work as well as that of others, that there is no evidence for the theory that "malignant" or "pale" hypertension is caused by the presence of pressor substances in the patient's blood. Pickering and Kissen[55] were unable to obtain evidence that patients with chronic nephritic hypertension are abnormally sensitive to adrenalin or evidence for the view that essential and nephritic hypertension are due to hyperadrenalinemia. Levitt[44] states from his observations that if the blood of patients with eclampsia and related disturbances does contain an increased amount of the hormone from the posterior lobe of the hypophysis, our present methods are unable to detect it. The occurrence of hypertension at the menopause and its reduction with theelin therapy[63] suggest studies of hormone excretion in hypertensive patients. Such titrations have been reported positive in Europe but could not be confirmed by Scarf and Israel[62] in this country.

The clinical application of the naturally occurring depressor substances in the body, such as acetylcholine, histamine, adenosine and related compounds has not been widespread because of toxic symptoms. They have been more popular in Europe, particularly the preparation, kallikrein, a pancreatic derivative, which has been given favorable reports. However, Nuzum, Elliot and Bischoff[46] in this country were unable to demonstrate a consistent effect and concluded that the preparation could not be regarded as a substitute therapeutic measure.

Much has also been said of the genesis of arterial changes in essential hypertension upon the basis of hypercholesteremia. Page, Kirk and Van Slyke,[50] however, in an analysis of the lipid content of the blood of such patients were unable to note any differences from normal in the cholesterol and cholesterol:phosphatide ratio in the absence of complicating disease.

The hypophysis has long been considered a possible factor in the development of both essential and secondary hypertension. A considerable mass of data is now available upon the subject. The demonstration that pituitary extract will raise blood pressure, and the separation of the oxytocic and vasopressor principles,[40] have led to much theorizing as to the part played by the pituitary gland in normal blood pressure as well as in hypertension. Houssay[38] has summarized the important observations in this controversy. In chromophobe adenoma of the pituitary and in Simmonds' disease, the blood pressure is often low. In acromegaly it is variable. In the syndrome described by Cushing as basophilic adenoma,[16a] characterized clinically by obesity, hypertrichosis, decreased sexual activity, hypertension and osteoporosis, the blood pressure is invariably elevated. Cushing feels that the hypertension may result from a specific secretion of the adenoma, from a stimulation of the pressor secretion of the posterior lobe by the adenoma, or from an action through some other gland. Although he favors the second explanation, others believe that the hypertension is due to adrenal hyperactivity, possibly brought about by the pituitary adrenotropic hormone.

Cushing's description of the above syndrome has stimulated a search for increases in basophilic cells in essential and other types of hypertension. Cushing[16b] has noted a basophilic infiltration into the posterior lobe in eclampsia. Butt and Van Wart,[11] however, were unable to correlate the basophilic infiltration with hypertension or eclampsia. Spark[65] agrees with the latter authors. He has found basophilic invasion of the posterior pituitary frequently in the absence of hypertension. Close[13] investigated the occurrences of pituitary adenomas in 280 glands at autopsy; 39 were found to contain an adenoma. None was basophilic. In serially sectioned glands, 10% had adenoma, 44% in cases of carcinoma of other glands. However, Costello[14] found adenomas in 20% of pituitaries studied at random, one-fifth of which were basophilic. Parsons,[52] in a gross anatomic and histologic study of 107 unselected pituitaries, was unable to correlate statistically the extent of invasion of the posterior lobe and systolic or diastolic pressure. Rasmussen[61] also could not relate basophilic infiltration to blood pressure. Leary and Zimmermann[42] serially sectioned 153 pituitaries from both sexes, all age groups, and from hypertensives and non-hypertensives. Slight to advanced basophilic infiltration occurred in 64.7% of all, including hypertensives and non-hypertensives. Significant infiltration occurred in 52 of 67 hypertensives and 22 of 86 non-hypertensives, showing this change to be much more common in the hypertensives.

The benefits of irradiation therapy in Cushing's syndrome favor the theory that the pituitary is the prime factor. However, the syndrome has been found with adrenal disease in the absence of pituitary changes and in at least 1 instance[45] with a thymic tumor associated with adrenal hypertrophy. In paroxysmal hypertension associated with chromaffin tumors of the adrenals[5] elevated epinephrine content of the tumor has been reported. Still one must remember that the adrenals have shown no anatomic changes in a number of patients reported with pituitary basophilism.[24] In 1 instance[29] pituitary adenoma occurred in association with carcinoma of the adrenal cortex.

The possible relationship of anterior lobe function to adrenal function and the occurrence in some cases of changes in both glands has not passed unnoticed. Houssay[38] has shown that the presence of the anterior pituitary is necessary for the development and maintenance of the normal anatomic and functional state of the adrenal cortex. Proper pituitary extracts have not only produced hypertrophy of the cortex, but small adenomas as well.[60] In Cushing's syndrome, the adrenals are hypertrophied or adenomatous, but not always so, and it has not been conclusively demonstrated that such changes are due to the adrenotropic hormone. Nor has an excess of adrenal or pituitary hormone been demonstrated in the blood.[38] Conclusive evidence of the etiologic importance of the pituitary gland in any type of hypertension is still lacking.

Experimental Hypertension of Renal Ischemia. Although experimental hypertension in relationship to the kidneys has been produced in many ways, such as partial nephrectomy, occlusion of the ureters, transplantation of the kidneys with subsequent irradiation, and the injection of aspartic acid,[21] its production in dogs and monkeys by the induction of renal ischemia by Goldblatt and his co-workers[26a,27,28] by constricting the renal arteries with silver clamps has become most popular because of the degree of hypertension produced as well as its simplicity and efficacy. The hypertension is persistent and has lasted, in some dogs, over 5 years.[26b] Constriction of varying degrees produces hypertension of varying severity. The similarity of this type of hypertension to that associated with renal disease in man had led to considerable work in the determination of its pathogenesis, particularly since the mechanism by which the diseased kidneys produce chronic hypertension is unknown. Indeed, there are those who deny the renal origin of hypertension at all.

Removal of the renal clamps following the production of hypertension by the Goldblatt method will cause a reduction in blood pressure to the original level as well as a return of kidney function. A unilateral clamp produces an elevated blood pressure which later tends to return to normal. However, removal of this kidney results in a fall in blood pressure to the normal range. Ischemia of the kidney is, therefore, important. The necessity for the presence of ischemic kidney tissue is attested by the fact that removal of one or both kidneys does not result in hypertension, and when both renal arteries are completely occluded the hypertension is not as great as with partial constriction[28] unless the occlusion is done in stages.

It is logical to expect an explanation for renal ischemic hypertension in the mechanisms already given for the hypertension of man, nervous influences, hormonal or chemical substances or both. Page[47c] has already shown that denervation of the kidney does not influence the development of hypertension by this method. Even complete sympathectomy, in 7 dogs,[23] did not prevent the development of hypertension nor was the level of hypertension materially affected during the course of total sympathectomy. Splanchnic section, and anterior root section, both used in the treatment of human hypertension, do not interfere with its development nor does it permanently reduce the hypertension previously produced by renal ischemia.[26b] Increased plasma volume and reflex changes in cardiac activity have been ruled out. The results, therefore, indicate quite conclusively that the mechanism of the hypertension of renal ischemia is not nervous.

The humoral theory immediately suggests itself as an alternative explanation. Goldblatt states "If the mechanism whereby constriction of the main renal arteries produces its effect on blood pressure be humoral and of renal origin, then in the case of the hypertension which also follows occlusion of both main renal arteries, it must be assumed that the natural accessory circulation through the capsule which may become more prominent in these circumstances, is sufficient to wash some hypothetical 'effective substance' into the systemic circulation through the main renal veins. . . . .The effective substance, for example, might act synergistically with a known pressor hormone from an endocrine organ, such as the hypophysis or adrenal. It is also possible for the hypothetical effective substance from the kidney to act by sensitizing the contractile elements of the arterioles to the action of the pressor hormone, or the reverse may be the case." It is also possible for such an effective substance to neutralize a hypothetical depressor substance in the circulating blood. Pressor effects of the extract of ischemic kidneys of dogs and hypertensive kidneys of man have been reported.[33,57] Extracts of normal kidneys and other organs have also given a pressor effect but not to the extent of these abnormal tissues. Page [47d] found no substance in the circulating blood of animals with renal ischemic hypertension which acts directly on the peripheral blood-vessels to cause vasoconstriction.

The relationship of the pituitary and adrenal glands to this type of hypertension has also attracted many workers. Page and Sweet[49] found that hypophysectomy reduced the blood pressure in Goldblatt dogs, but that preliminary hypophysectomy did not prevent the rise in blood pressure, which tended to be transient, however. Furthermore, hypertension of this type can develop in the absence of the adrenal medulla.[28] With bilateral adrenalectomy blood pressure did not rise, but the period of survival was short. Even with supportive treatment, this operation interfered with the development and maintenance of the hypertension, but with added substitution therapy (intravenous cortical extract) a significant but not great rise in blood pressure occurred.[26b] The mechanism of this interrelation in the production of hypertension is not yet known. All that can be said, as yet, is that the evidence indicates that the hypertension of renal ischemia is of renal humoral origin.

The most important question to the clinician in regard to the hypertension of renal ischemia is the extent to which these results can be carried over from animals to the patient. Little can be said on this point at the present time except by inference. The reduced blood flow of experimental ischemic hypertension may possibly be compared to that of arteriolar disease of the kidneys in man.[26b] The return to normal of the blood pressure when the silver clamp is released has been compared to the possible results of operations on the nervous system in relaxing arterioles and correcting the possible ischemic state. Such a supposition is, as yet, not at all established, and the work on renal denervation already cited[47a] speaks against it as does the failure of the urea clearance to change appreciably with splanchnic section. The unimportance of the nervous system in this type of nephritis is in keeping, however, with the work of Prinzmetal and Wilson and of Pickering, showing the non-nervous nature of the fundamental defect in human hypertension.

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PEDIATRICS

UNDER THE CHARGE OF
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TUBERCULOSIS IN CHILDHOOD.

THE subject of tuberculosis in childhood is such an extensive one that a proper consideration of even the most recent contributions in the literature would be very lengthy. Consequently, in this review an attempt will be made only to present a few of the more salient facts that must be stressed in order to understand something of the present-day status of this disease in infancy and childhood.

That there exists a difference between tuberculosis in childhood and tuberculosis in adult life is generally conceded, although Medearis[12] says that evidence is steadily accumulating that the adult type of the disease can and does develop endogenously from the childhood type. The frequency of tuberculosis infection in children as shown by the percentage of positive reactions to tuberculin tests in various surveys in this country has averaged roughly 10 to 15% of all children up to 15 years. The question of tuberculin tests and the value of positive and negative reactions has caused much argument on both sides. According to Medearis there are three general groups of tuberculin tests: 1, A cutaneous scratch or abrasion with a rather blunt scarifying instrument and inoculation of the wound with Koch's old tuberculin, which is known as the Pirquet test; 2, an intradermal test whereby 0.1 cc. of dilution of Koch's old tuberculin is injected intracutaneously, which is known as the Mantoux test; and 3, some modification of an inunction method. A positive reaction is indicated in the first two methods by a surrounding area of erythema appearing in about 48 hours and persisting at least 5 or 6 days. In the third method, a positive reaction is indicated by a number of papular efflorescences appearing in from 3 to 5 days and remaining visible for about 2 weeks. Of these tests the Mantoux is by far the most sensitive. Mcdearis urges a wider use of the tuberculin test. Every child giving a history of home contact with tuberculosis should be tested. Any child with an unexplained temperature or with subnormal weight gain deserves a tuberculin test. The Mantoux should be a routine procedure in every hospital admission to the pediatric service. Every positive reactor should have a roentgenogram of the chest and the interpretation of the plate should be made by a physician trained in the Roentgen ray diagnosis of tuberculosis. In every case in which primary tuberculosis complex has been diagnosed, an adequate medical follow-up should be given with proper hygiene and dietary supervision and examination at intervals frequent enough to assure detection of any developing adult type disseminated lesions so that early and effective therapy can be established.

Stewart and Dyson[18] state that the Mantoux tests with old tuberculin and purified protein derivatives in doses of unequal potency agree in showing that, as a rule, children are more sensitive to tuberculoprotein than adults and that this difference between the two age groups is due to the occurrence among adults of a disproportionately large percentage of patients with relatively small areas of reaction to tuberculin. They offer also the suggestion that the difference in allergy noted between the two age groups is a product of a general tendency for sensitiveness to diminish slowly as the postinfection time elapses. The sensitiveness to tuberculoprotein induced in the tissues by tuberculous infection is an extremely variable and moderately unstable immunologic change.

Law and Cory[11] found the behavior of purified protein derivative in its two standard test doses potent and reliable in comparison with three dilutions of potent old tuberculin in about 3000 tests. The first strength of purified protein derivative was 0.00002 mg. and there were more reactors than with old tuberculin in a dilution of 1 to 1000. The second strength of purified protein derivative found twice the number of reactors shown by old tuberculin used in a dilution of 1 to 100. Purified protein derivative is well adapted to accurate quantitative tests and seldom causes necrotic skin reactions. It is also very well suited for general use and for epidemiologic studies related to the control of tuberculosis.

Kayne[9] recommends 1 to 10,000 dilution for the initial injection of the Mantoux test with the result read on the third day. If the reaction is negative or doubtful the test is concluded with a 1 to 100 dilution. He agrees that there should be at least a 10 mm. wheal of erythema and swelling after 48 or 72 hours for the test to be called positive. In a child less than 2 years a positive reaction to the Mantoux test should be regarded as indicating the presence of an active tuberculous focus, unless the opposite is proved by further investigation. The reaction to the Mantoux test cannot be regarded as negative unless a dilution of 1 to 100 has been used.

A form of tuberculin testing that may have little general use is the plaster test. As used by Anzén,[1] after the skin, usually that over the manubrium sterni, is cleansed with ether, a plaster is applied as a control and about 1 cm. below this the tuberculin plaster is applied. For infants and nervous children it seems expedient to apply an ordinary adhesive plaster over the other two to prevent them from being pulled off. The reaction is read after 48 hours. In the positive reaction, the skin beneath the tuberculin plaster is found to present, sparingly or more closely according to the degree of the reaction, highly red papules the size of a pinhead. In the negative reaction, the skin remains unaltered. Occasionally a reaction may also be obtained under the plaster used as a control. The exceedingly few cases in which this occurs have been in tuberculous patients with exudative diathesis. The plaster used in this test contains 1 drop of tuberculin per square centimeter.

Another method that may be helpful in the diagnosis of tuberculosis in children is the study of gastric washings for the tubercle bacilli. Rothstein[16] says that the finding of tubercle bacilli in the gastric contents, as determined by the production of tuberculosis in a guinea pig inoculated with the sediment obtained from the gastric washings, is indicative of the presence of an active tuberculous lesion. This focus is usually either in the lung or in a hilar or tracheobronchial lymph node which has ulcerated into the bronchus. Tubercle bacilli were demonstrated in 7 patients (8.14%) of a series of 86 infants and children with positive cutaneous reactions to tuberculin in whom no recognizable evidence of tuberculosis could be demonstrated on physical or roentgenographic examination. Examination of the gastric washings for tubercle bacilli by the inoculation of a guinea pig with the sediment should be done for all infants and children with positive cutaneous reactions to tuberculin even if no evidence of tuberculosis has been found on physical or roentgenographic examination.

Armand-DeLille[2] says that although many points still remain obscure, it is possible to say that two principal conditions account for the differences in location and form in adults and in children. The adult patient has allergy and this tends to produce localization. The child, and especially the infant, has primary infection, which becomes generalized, and he dies from disseminated tuberculosis or from meningitis. According to his statistics, 60% of the infants and children in contact with tuberculous parents present characteristic tuberculous evolution before the death of the tuberculous parent, and two-thirds of them (40%) die from acute forms such as miliary or tuberculous meningitis and only one-third of these (60%) present chronic localizations. Forty per cent appear to be clinically sound, but they have a positive Pirquet, and many present small shadows in the lungs or in the hilus from an inactive primary affection which may wake up later at the time of puberty and adolescence, and be the beginning of a chronic pulmonary tuberculosis. In adults, the lung seems to be the organ that offers least resistance to tuberculosis, perhaps because its capillary system constitutes a kind of screen for all the tubercle bacilli carried by the blood stream. Also in the adult it seems that, with the exception of the kidneys and the genital organs, most of the tissues of the body have acquired a special resistance against the infection. In the case of children, however, where the organs are still growing, those that are developing the most rapidly appear to be the least resistant to the bacillus. As the child gets older he, like the adult, more often presents reinfection which is usually endogenous.

The term primary infection has been used. Hancock[8] defines primary tuberculosis as those pathologic changes which occur at the points of localization of the first infecting dose of tubercle bacilli and the systemic results of these changes. It does not include any of the superinfection types, even though these may be caused by the identical organisms which caused the primary lesion, either at the same location or at distant points to which they may have escaped. Superinfection may be either endogenous or exogenous, but in either event it must be sharply differentiated from primary infection, the difference being not in the infecting organism but in the host.

According to Myers, Harrington, Stewart and Wulff[14] the early Roentgen appearance of the parenchymal lesions of the first infection type of tuberculosis may be indistinguishable from that of the reinfection type or of pneumonia. A period of observation is necessary in most cases. In the absence of significant symptoms when a parenchymal shadow persists for one month or longer in a child who is sensitive to tuberculin, it is due usually to the tubercle bacillus. After a longer period of observation, if the shadow gradually disappears to be replaced by calcium shadows in the parenchyma or in the region of the hilus, it may be regarded as representing the first infection type of tuberculosis. The shadow characteristic of the pneumonic stage usually persists for several months or for a year or more. They may then disappear to be succeeded after months or years by the appearance of calcium shadows or fibrous strands. It is a diagnostic point that throughout the course of the disease significant symptoms are usually absent. This benign course is so characteristic of first infection tuberculosis that even though it appears in young children and reaches considerable proportions, it is not of itself a serious condition unless secondary complications arise as the result of endogenous superinfection or reinfection. This also holds true of this type disease as it occurs in young adults. The immediate prognosis of the first infection type of tuberculosis is excellent, and there is no indication for treatment except in the rare cases in which the condition is febrile.

The evolution of the first infection type of tuberculosis is described by Myers.[13] He suggests that neutrophils ingest tubercle bacilli in the blood stream and, together with the ingested bacilli, focalize in the small alveolar capillaries. About these focal accumulations large numbers of exudative mononuclears accumulate, which in turn become phagocytic, ingesting both bacilli and neutrophils. This becomes the epithelioid cell of the tubercle. This focalization and walling off before sensitization appears may be an important factor in making primary tuberculosis benign. Following the introduction of tubercle bacilli into the organism the tissues become sensitive to tuberculoprotein. This sensitivity is manifested by a positive tuberculin reaction in from 3 to 7 weeks after infection. Following sensitization, if reinfection from endogenous or exogenous sources occurs, tuberculosis of the usually benign first type may be stimulated to activity and disease of the destructive type develop.

Schick[17] points out that the distinctive features of the childhood type of tuberculosis are the result of the reaction of the virgin tissues of the child to the invasion of the tubercle bacillus. Infection occurs usually by inhalation but occasionally by other routes such as by ingestion. The tuberculous lesion may be recognized microscopically in from 2 to 3 weeks, and clinical signs may appear in from 4 to 6 weeks. The primary lesion usually heals readily, remaining active longest in the glands. A clinical arrest of the disease requires at least 2 to 3 years. In favorable cases, the disease remains limited to the primary complex or primary focus in the alveolus or small bronchi and the regional lymph glands. The secondary stage or further extension may occur by dissemination of the bacilli from the primary focus by way of the lymphatics, the blood stream or the bronchi. The extent and seriousness of this secondary invasion is determined by three factors: the intensity of the invasion, the resistance of the subject and the organ attacked. In spite of the evidence brought forward to the contrary, Schick believes that the original idea must be maintained that the primary complex has a beneficial effect on later occurring superinfection.

With reference to the pathologic sites of the infection Blacklock[5] studied a series of 2500 autopsies. He found 378 tuberculous lesions in this group of children, varying in age from 1 day to 13 years. Tuberculosis was the cause of death in 95.2% of 253 subjects under 3 years and in 74.4% of 125 children over 3 years. Girls of all ages were more often infected than boys. The primary sites of infection were as follows: thorax, 63.4%; abdomen, 32.4%; cervical region, 8%; and undetermined, 7%. Most of the children with primary intrathoracic tuberculosis died of generalized infection and this was slightly more common in children under 3 years than in those older than 3 years. Among children living in the reported area intrathoracic tuberculosis is a relatively fatal disease especially in children less than 3 years. The primary site of the tuberculous infection was in the abdomen in 123 cases, with a relative incidence greater in children over 3 years than in those under that age, but more deaths occurred in the younger children. Intestinal ulceration occurred in 22 cases. In 74.4% of the children under 3 years and in 29.3% of those over this age, generalization of the infection caused death. Tuberculous disease limited to the abdomen caused more deaths than similar disease confined to the lungs. In cases of abdominal lesions causing death, human strains of the bacilli were isolated in 11 instances and bovine strains in 47. From children not dying of the abdominal disease 2 human and 13 bovine strains were obtained. In the entire series of 236 strains isolated, 29.2% were bovine, the percentage varying from 24.4 in children up to the age of 1 year to 35.7 during the second year and thereafter, gradually increasing to 25.3% in children between the ages of 6 and 13 years.

In regards to the occurrence of the bovine and the human types of tubercle bacillus infection in man, Szüle[19] says that according to Koch bovine tuberculosis was less virulent for man than the human type. This belief was based on the fact that the presence of bovine tuberculosis in the human sputum had never been proved. Since then such bacilli have been found on numerous occasions but this observer found them only twice in 201 cases and he does not believe that the bovine type of tuberculosis bacillus is transformed into the human type when it infects man but that it retains its original properties. Because of less infection among dairy herds the occurrence of this type of tuberculous infection in childhood as well as in adult life has decreased. However, Tobiesen, Jensen and Lassen[20] have reported 26 cases of bovine pulmonary tuberculosis. Of these, 10 were under 5 years and none over 32 years. In only 1 instance in this group could tuberculosis be demonstrated in the home. Of the 26 patients, 13 had been drinking raw milk for some time, while only 3 denied having taken raw milk. The pulmonary disease was preceded by cervical adenitis in 11 of the cases. The pulmonary processes did not show any distinctive features in the roentgenograms. In 18 cases the tubercle bacilli were obtained by gastric washings alone. Of the 6 patients that died during the period of observation all showed generalized tuberculosis. Of these, 3 were under 5 years, 2 between 5 and 15 years and 1 over 15 years, so that it would seem that the bovine type of pulmonary tuberculosis was as serious in the age period below 5 years as the human type.

The problem of preventing the dissemination of tuberculosis is a great one. It is possible to isolate or segregate only a small portion of the active open cases, consequently the prevention of the spread of the disease has been only relatively successful. The danger of contamination is especially great in infancy and childhood. For that reason the prophylactic inoculation of children with the B.C.G. vaccine as devised by Calmette and Guérin was received with the highest expectation. Question arose as to the dangers of this procedure and as a result the use of this method has not become as widespread as was expected. According to Rist,[15] only children having a negative reaction to tuberculin are suitable for inoculation with B.C.G. There is practically universal agreement that in infants its use is innocuous. The difficulty has been to determine how universal the protection is among vaccinated children. There has been considerable criticism as to the methods used in statistical computation as regards the influence on the death rate in tuberculosis. Oral administration has been used but it does not regularly immunize all children, so that it must be regarded as an uncertain method of vaccination.

Clawson[7] carried on a series of experiments on immune reactions in experimental tuberculosis. The purpose of his study was to determine an experimental basis for the safest and most efficient method of using the Calmette-Guérin bacillus in developing resistance of bovine and human tuberculosis. Another consideration was the relation of the reactions included in immunity to the pathogenesis of tuberculosis. In conformity with the course pursued in previous experiments on vaccination with streptococci, the B.C.G. was administered as living organisms subcutaneously and intravenously and as heat-killed organisms in the same ways. The vaccine so administered was studied in respect first to safety and then as to resistance. No mechanical injuries, such as bacterial emboli or any other kind of tissue-injury, were observed at any time from vaccinating many animals by each of the four methods. No toxic results, either immediate or delayed, were noted in the normal animals after vaccination. With large doses given intravenously to animals already allergic, extreme collapse and death within 24 hours took place, but ordinary doses were not accompanied by toxic effects in the allergic animals. Subcutaneous injection of the vaccine into allergic animals had no ill-effects. In allergic animals vaccinated with relatively small doses intravenously, small non-progressive tubercles frequently developed in the lungs, liver, and spleen. It would seem in the light of present observations that vaccination should be limited to those not having a positive tuberculin reaction. It would be an advantage if it is found that allergic animals can be safely vaccinated intravenously, for in the process of vaccinating the allergic animals they are desensitized, at least for a time, and resistance is increased. Allergy was studied as a factor in safety and also in respect to its influence in the pathogenesis of tuberculosis. The frequency and degree of allergy was greater after vaccination by methods in which the living organisms were injected, but even by these methods allergy did not develop in all animals. A relatively small amount of allergy was produced in the animals given subcutaneous injections of heat-killed organisms. No animals vaccinated intravenously with heat-killed organisms ever became allergic. It was found that severe allergy following vaccination disappeared in about 3 months and less severe allergy in less time—sometimes in as short a time as 1 month. This disappearance of allergy was probably more rapid than in persons in whom allergy is so frequently due to arrested active lesions. It seems probable that allergy, especially of the lesser degrees, which develops in the course of vaccination with B.C.G., should not be looked on as a serious handicap. Allergy in association with vaccination and probably with the development of a tubercle appears much earlier than is generally thought. It has been found to appear in from 1 to 3 weeks. In these experiments, if allergy had not appeared in 3 weeks after the last injection of the vaccine, it was found that it would not occur.

After 8 years of careful study both clinically and in the laboratory, Kereszturi and Park[10] are convinced of the harmlessness of the B.C.G. vaccine. They injected large amounts of living B.C.G. organisms into between 400 and 500 laboratory animals. All animals remained free of tuberculosis except 1, and in that 1 accidental infection could not be excluded. Clinically, the vaccine was administered to 175 infants who were not known to have been exposed to tuberculosis, with the possible development of clinical tuberculosis in but 1 of the entire group. Of 515 children vaccinated with living B.C.G. organisms and exposed to tuberculosis, only 5 contracted the disease. From these patients organisms of the human but not of the bovine type were recovered. In 27 cases, the virulence of the B.C.G. strain recovered from cold abscesses caused by the vaccination could not be shown to have been increased by living in the human body for periods of from 1 to 10 months. The parenteral administration of the vaccine seems to be more effective than the oral since the tuberculosis death rate decreased to one-half when the oral method was used and to one-fourth when B.C.G. was injected intracutaneously. Since this procedure is harmless and increases considerably the resistance to tuberculosis, its use should be urged as a public health measure in those who have not yet become infected and who may later become exposed to tuberculosis in their own families.

Aronson and Dannenberg[3] undertook a study to determine the value of B.C.G. vaccine in newborn infants living in families with known cases of manifest tuberculosis. These were given the vaccine orally, while infants, similarly exposed but too old to be vaccinated by mouth when first observed, served as controls. They gave 30 mg. of the B.C.G. vaccine by mouth to 43 white and 27 colored infants. As controls there were 114 white and 53 colored infants. Of 41 children who remained in contact with persons having tuberculosis and who were vaccinated in the first 10 days of life by the peroral administration of B.C.G. vaccine, 1 died of tuberculosis, while of 84 unvaccinated children living under comparable conditions, 10 died from the disease. Of 15 children vaccinated with B.C.G. vaccine who remained in contact with persons having tuberculosis but whose sputum did not contain tubercle bacilli, none died of tuberculosis, while of 45 unvaccinated children living under comparable conditions, 2 died of tuberculosis. No deaths from tuberculosis occurred in the children studied who were not exposed to persons known to have manifest tuberculosis, either among the vaccinated or among the unvaccinated children. Of children in contact with tuberculous persons whose sputum contained tubercle bacilli, 81.6% of 38 vaccinated children and 78.5% of 79 unvaccinated children reacted positively to an intracutaneous injection of tuberculin. Among 14 vaccinated and 44 unvaccinated children in contact with persons having tuberculosis whose sputum did not contain tubercle bacilli, 92.8% of the vaccinated and 36.4% of the unvaccinated children reacted to tuberculin. Of children living in contact with tuberculous persons whose sputum contained tubercle bacilli, 16.6% of 36 vaccinated with B.C.G. and 56.6% of 83 unvaccinated children presented roentgenologically demonstrable lesions in the lungs. Among the children living in contact with persons with tuberculosis whose sputum did not contain tubercle bacilli, no pulmonary lesions demonstrable by the Roentgen rays were observed in the 13 who had been vaccinated, but 5% of the 40 unvaccinated presented roentgenologic evidence of pulmonary lesions. No lesions demonstrable by means of the Roentgen rays were found in the 8 vaccinated or 36 unvaccinated children not in contact with persons known to have tuberculosis. These results indicate that the administration of B.C.G. vaccine to newborn children exposed to patients having manifest tuberculosis may prove of value in reducing the mortality from this disease in infancy and childhood.

While the value of B.C.G. vaccine in the prevention of tuberculosis in children and in the decrease of the mortality rate of the disease is admitted by many, some observers are somewhat skeptical. Boynton[6] made an analysis of the deaths from tuberculosis in Minnesota from 1915 to 1932. In this state where B.C.G. vaccination was not used the mortality rates in children from tuberculosis were lower and had decreased more than the rates in Sweden, where the vaccine was used. He found that although there had been a decrease of 80% in the mortality rate in infants under 1 year, the death rate still remained higher in this age group than in any group under the age of 15 years. Tuberculosis of the lymph nodes, bones and joints was a negligible cause of death in children under 15 years. Tuberculous meningitis, pulmonary tuberculosis and miliary tuberculosis were the more important causes of death.

Beaven[4] studied 4982 children between 1926 and 1934. As a result of his study he concluded that tuberculosis among children was decreasing rapidly. He believes that if the rate of decline continues, it will soon be a rare disease. Every one hopes that this prophecy will be fulfilled. He does not believe that there has been attenuation of the organism causing tuberculosis, but he feels that there are fewer individuals infected. If this is actually the case throughout the country, too much praise cannot be accorded public health officials and the activities of the Red Cross and similar organizations.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 15, 1937

Studies in Blood Volume and Blood Pressure Following the Extravascular Administration of Fluid in Rats. J. Q. GRIFFITH, JR., and R. CAMPBELL (Robinette Foundation, University of Pennsylvania). Forty-one albino rats were injected intraperitoneally with physiologic saline in amount equal to 15 cc. per 100 gm. body weight. After 24 hours 11 animals had an elevated blood pressure, and 30 did not. Of the hypertensive animals, 4 had evidence of blood dilution based upon change of refractive index of plasma, and the remaining 7 had an increased blood volume. Of the animals with normal pressure, 18 had no evidence of dilution, or of increased blood volume; 8 had evidence of some dilution or of increased blood volume, but less than was present in the hypertensive animals; 4 showed evidence of dilution, or of increased blood volume, to a considerable degree. The 4 in this last group were all young animals. In no case did a vascular hypertension occur without evidence of plasma dilution or of increased blood volume. Under the conditions of the experiment, blood pressure and blood volume appear to vary directly.

Glucose Tolerance in Normal Rats. V. V. Cole and B. K. Harned (Laboratory of Pharmacology, Woman's Medical College of Pennsylvania). Glucose tolerance tests were carried out on male rats from two different colonies. The glucose tolerance tests on Wistar rats were found easy to duplicate and consistent over a long range in age (at least 90 to 400 days). Rats under 60 days of age demonstrated a higher glucose tolerance than the older animals. The average fasting blood sugar of the Wistar rats was 67 mg. %. After injection of glucose the blood sugar rose to a height of about 170 mg. % at the half hour. By 2 hours after administration the blood sugar had fallen to 113 mg. %. There was no essential change between the second and fifth hours. Another strain of rats in the same laboratory gave inconsistent glucose tolerance results. After 2 months of age, 60% of the curves were diabetic in type and 46% of all animals showed only diabetic curves. The technique used for these studies consisted of a 16-hour fast followed by intraperitoneal injeetion of 3.5 gm. per kg. of glucose in a 10% solution. Blood samples were taken before injection and $\frac{1}{2}$, 1, 2, 3 and 5 hours afterward.

Hyperglycemia Produced by a Synergistic Action of Strychnine and Physostigmine. B. K. Harned and V. V. Cole (Laboratory of Pharmaeology, Woman's Medical College of Pennsylvania). Appropriate quantities of strychnine and of physostigmine administered to normal male rats exert a synergistic hyperglycemic action offering therapeutic possibilities in the treatment of a selected type of hypoglycemia. The action is accomplished through the liberation of adrenalin and disappears in rats with demedullated adrenals. In the quantities in which the drugs were used no undesirable side effects were observed.

The technique consisted in employing the glucose tolerance test as outlined by the authors. The drug injection immediately followed the 1-hour blood. The differences between the blood sugar values obtained with and without the drugs served to measure the effect of the drug.

The data were obtained on 22 adult male rats. Each animal was subjected to the following glucose tolerance tests: (1) Without drug; (2) with strychnine; (3) with physostigmine; (4) with strychnine and physostigmine. The drugs were administered subcutaneously and the quantities employed were always 0.52 mg. per kg. for strychnine sulphate and 0.1 mg. per kg. for physostigmine salicylate.

One hour after the administration of the drugs strychnine produced a small elevation in the blood sugar, physostigmine a definite elevation, and the combination of physostigmine and strychnine produced a hyperglycemia significantly greater than the sum of the effects produced by the separate drugs. The synergistic effect was more pronounced on the second hour and persisted for 4 hours. The synergistic action amounted to 20 mg. % of blood sugar on the second hour but we believe that optimal conditions will show a greater rise.

The Conduction of Labyrinthine Impulses to the Cerebral Cortex. E. A. Spiegel and J. B. Price (Laboratory of Experimental Neurology, Temple University). The conduction of labyrinthine impulses to the higher centers was studied in cats, by recording the cerebellar and the cerebral cortical action potentials after stimulation of the labyrinth by rotation. A special apparatus was built permitting artificial respiration and the connection of the electrodes with the recording galvanometer to be retained during rotation. Stimulation of the labyrinth by rotation induces a functional change in the cerebellar cortex, as shown by an increase of the amplitude and number of the fast oscillations led off from the cortex of the vermis cerebelli. Changes in the electrocorticogram similar to those induced by stimulation of other sensory nerves (increase of the fast oscillations, inhibition of the slow waves) may be elicited by the labyrinthine impulses, even if the cerebellum is extirpated, and if this operation is combined with severance of the posterior longitudinal fasciculus in the anterior third of the pons. It is inferred that the labyrinthine impulses may reach the cerebral cortex not only by way of the cerebellum-ruber system and by connections of the posterior longitudinal fasciculus with the nucleus ruber, but also by pathways outside these systems. Vestibulo-reticulo-thalamic pathways and connections between the vestibular and the cochlear tracts come into question.

The Rôle of the Upper Small Intestine in the Control of Gastric Secretion. The Effect of Neutral Fat, Fatty Acid, and Soaps. The Phase of Gastric Secretion Influenced and the Relative Importance of the Psychic and Chemical Phases. HARRY SHAY, J. GERSHON-COHEN and SAMUEL S. FELS (Samuel S. Fels Fund and Gastro-intestinal Division, Medical Service 1, Mt. Sinai Hospital). Our studies have consistently shown a marked depression of gastric secretion in man when neutral fats, fatty acids and soaps, in proper concentration, were instilled into the duodenum beginning at the time the mouth meal was taken. All secretory fractions were involved: acid, chlorides and enzymes. This depression of secretion continued for a considerable period of time after the instillation of the stimulant was stopped. A secondary sharp rise in gastric secretion was frequently observed after the oil effect was overcome. We have not been able to confirm the opinion that this secondary rise in secretion was dependent upon the formation of soaps in the upper intestine whose action was supposed to cause stimulation of gastric secretion. The duodenal instillation of a representative soap, sodium oleate, in proper concentration (15%), produced, as did oil, first, depression of secretion, followed by a rise in secretion.

From a study of the effect upon gastric secretion of many agents other than fat instilled into the duodenum, we frequently saw the sharp secondary rise of gastric secretion following the initial depression. The result obtained with 40% glucose was used to illustrate the action of agents other than fat or fat derivatives. Such results obviously militate against any specific gastric stimulating effect previously ascribed to soaps in the upper intestines.

By the use of duodenal instillates of different concentrations (2% and 15%) sodium oleate, and varying amounts of the same concentration, we saw a difference in the threshold of response of the gastric motor and secretory mechanisms as influenced from the intestine. The motor mechanism appeared to have a lower threshold than did the secretory. The mechanism of enzyme secretion, too, appeared to be influenced differently from the acid mechanism. This was seen in the almost consistent earlier rise in enzyme concentration after the duodenal stimulant was stopped.

The question was raised whether the secondary rise in the gastric secretion following the secretory depression after the duodenal instillation of oil might represent a discharge of secretion stored up during the depression period.

We believe that the duodenal influence upon gastric secretion was exerted chiefly if not entirely upon the psychic phase of gastric secretion; further, that this phase represented the important one in gastric secretion. These opinions are based upon experiments in which the interval between the beginning of the meal and the duodenal instillation could be increased to a point where the duodenal instillation became ineffective; upon the prevention of the stimulation of gastric secretion during insulin hypoglycemia; and upon the failure of duodenal stimulation to prevent a rise in gastric secretion following histamine injection.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
FEBRUARY, 1938

ORIGINAL ARTICLES.

CULTURE OF HUMAN MARROW: AN IMPROVED APPARATUS FOR LARGE SCALE CULTURE.

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In a previous article,[2] an apparatus was described which supplied the functions of a lung, kidney and circulation for marrow and would accommodate volumes of 10 to 20 cc. This apparatus was complicated and expensive to build. The purpose of this article is to describe a much simpler apparatus which greatly increases the scale of the cultures and has all the advantages of the original method and, also, a number of others.

Method. The apparatus is assembled (Fig. 1) from 5 two-liter Pyrex aspirator bottles,* Pyrex standard wall glass tubing, and pressure tubing. Its operation is tested and the volume of fluid in Bottle 1 at the level of the inlet orifice of 4 is determined. All connections must be gas tight under a pressure of at least 60 inches of water. The number of drops per cubic centimeter from Tips 21 and 11 is determined. The temperature of the water bath should be adjusted, with water instead of medium flowing through the apparatus at the rate desired for use with the marrow, so that the temperature as determined on the fluid within 1 after a period of time for equilibrium to be reached is 37.5° C., or the temperature desired for the purposes of the experiment. As a rule, the temperature in the flask is about 1° lower than that in the bath but this should be determined for each experimental condition. The apparatus is then disassembled at convenient joints and Bottles 1, 5 and 9 with their connections as far as 23 are sterilized in the autoclave, the free ends having been wrapped in paper or gauze. The gas system, including Bottles 13 and 19 and their connections, do not need to be sterile. The apparatus is reassembled, using aseptic technique, flaming the

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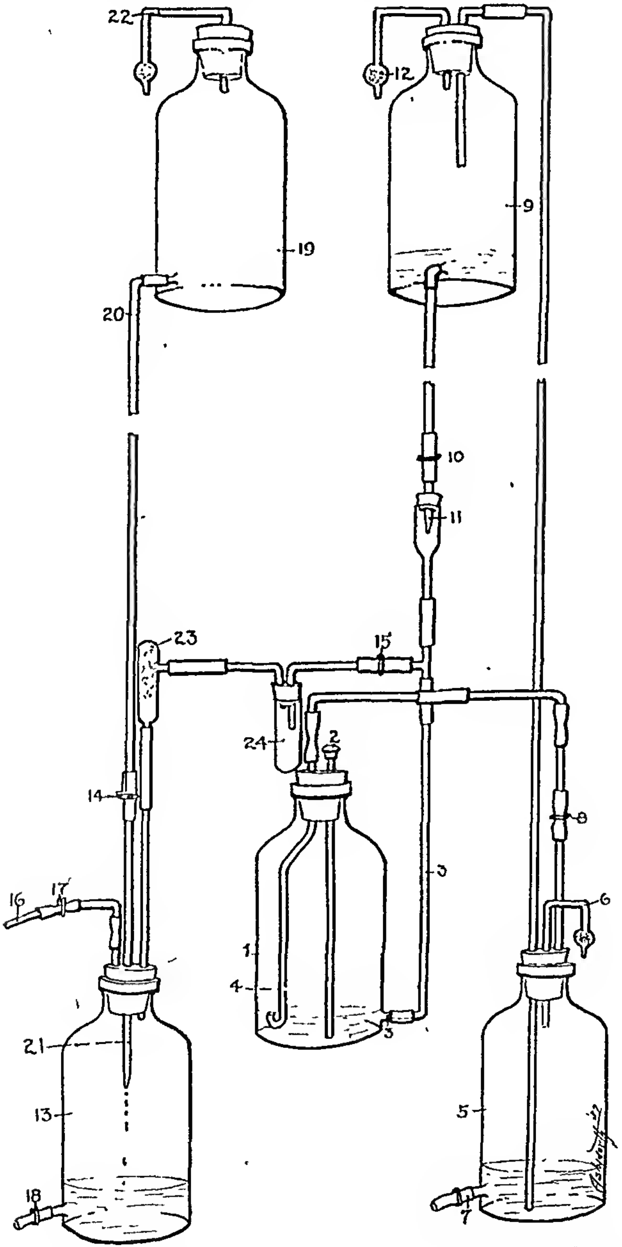
* Any size of container may be substituted for these without altering the principle of the method.



ends of glass tubes and pouring 70% alcohol on the rubber tubing before making each connection. The marrow, obtained as previously described,[1] is introduced into Bottle 1 through vaccine Cap 2.

Medium[1] is introduced with a syringe and needle through rubber Tube 7, previously sterilized with alcohol, into Bottle 5. Screw Clamp 8 is closed and, by compressed air or a bulb, such as that on a blood-pressure manometer, air is forced in through 6 until the medium is all transferred to Reservoir Bottle 9. The bulb is disconnected from 6 and the rate of flow of the medium from Reservoir 9 is adjusted by Screw Clamp 10, counting the number of drops per minute from Tip 11 which has been previously calibrated so that the cubic centimeters per hour or 24 hours can be calculated. Any gas mixture desired[1] is made up in a spirometer and introduced into Bottle 13 by closing Screw Clamps 14 and 15 and filling Bottle 13 completely full with 5 to 10% sulphuric acid.* The outlet of the spirometer is attached to Inlet 16 and the gas is allowed to flow into Bottle 13 by opening Screw Clamps 17 and 18, collecting the acid as it flows out in Reservoir Bottle 19 which is disconnected for this purpose. When 13 is almost empty, 18 and 17 are closed, 19 is placed back on its shelf and attached to outlet Tube 20; 14 is opened and the rate of flow of acid is adjusted by the number of drops per minute of the calibrated Tip 21 to give the desired rate of gas flow; 15 is opened. The gas leaving Bottle 13 is filtered through sterile Cotton 23, passes through Trap 24, and in passing down Tube 3 equilibrates with the medium flowing through the same tube as it enters culture Bottle 1.

The medium[1] and gas enter through fine Tip 3. Since the medium is slightly cooler than that in the flask, it flows across the bottom and then gradually rises to the surface. The pressure of the inflowing medium and gas forces the used medium and gas out through Tube 4 into Reservoir 5 from which the gas escapes through cotton-filled Bulb 6 and may be collected if desired.

* This prevents growth of molds and bacteria and dissolves less carbon dioxide than water.

LEGEND FOR FIG. 1.

FIG. 1.—Improved marrow culture apparatus. 1, 5, 9, 13 and 19 are two-liter Pyrex aspirator bottles; 5 and 13 rest on the laboratory shelf or table, and 9 and 19 rest on a shelf about 47 inches higher. 1 is supported in a constant temperature water bath which is not illustrated. 2 is a rubber vaccine cap, fitted tightly on the end of a Pyrex glass tube touching the bottom of Bottle 1. Note that Pyrex Tube 3 terminates in a fine tip so that the small bubbles of gas which escape do not tend to stir up the cells. Note that the tip of Pyrex Tube 4 is turned upward and is at the farthest point in the bottle from Inlet 3. Its position in relation to the bottom of the flask regulates the volume of medium and permits a skimming action in the outflow so that no cells are lost. 6, 12 and 23 are bulbs filled with cotton which are autoclaved along with the apparatus. 22 is also filled with cotton but need not be sterile. The purpose of the cottom filters is to prevent dust from entering Bottle 19 and to prevent bacteria from entering Bottles 1, 5 or 9. 7 is heavy pressure tubing which after sterilization with 70% alcohol may be punctured diagonally with a 20-gauge needle for introduction of medium just as though it were a vaccine cap. 8, 10, 14, 15, 17 and 18 are screw clamps, of which 10 controls the rate of flow of media and 14 the rate of flow of gas. 24 is a trap to prevent moisture from reaching the sterile cotton in 23. Since the gas mixture and media both flow through Tube 3, there is abundant opportunity for equilibrium of the gas mixture with the medium in this tube.

Culture Bottle 1 may be tilted at any time so that the inlet of 4 is above the level of the liquid, thoroughly mixed by shaking, and marrow culture aspirated through 2 for counts and examination as previously described.[1] The total numbers of any cell type present in the culture may be calculated by multiplying the number per cubic millimeter by the volume of the culture in cubic millimeters (in our cultures, 210,000 c.mm.). No semipermeable membrane is necessary because the cells settle out and only the surface layer of fluid flows out through Tube 4.

The method permits a rapid, controlled rate of flow of the medium past the cells and a rapid, controlled rate of gas supply. The medium from either Bottles 1, 9 or 5 may be aspirated with a sterile syringe and needle through the pressure tubing at the outlet at any time for chemical, bacteriologic or serologic examination. The medium may be used over and over again by pumping it as described above from Bottle 5 to Bottle 9. Gas may be collected at 6 for analysis.

Summary. An improved apparatus for culture of human marrow in bulk is described. This apparatus is much simpler and less expensive to construct than the original apparatus. The capacity is over 200 cc. and might be increased still further by use of larger bottles. The device permits control of temperature, pH, oxygen and carbon dioxide tensions, composition of the medium, and the removal of waste products without loss of cells. There is a continuous flow of both gas and medium permitting conditions within the culture flask to be kept constant at all times. It permits removal of mixed samples of culture at frequent intervals in quantities sufficient for any type of hematologic, chemical, bacteriologic, or serologic examinations done on blood.

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STUDIES OF GAUCHER CELLS BY THE SUPRAVITAL TECHNIQUE.

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Fresh (unstained) preparations of living Gaucher cells were studied (by Marchand[8], Risel,[9] Mandlebaum,[6] and others) many years ago. The purpose of this report is to describe living Gaucher cells as seen in supravital preparations.

Five patients were recently admitted to this hospital, with many of the typical clinical signs of Gaucher's disease as described by Welt, Rosenthal and Oppenheimer.[13] These signs were pingueculæ, brownish pigmentation of the exposed parts of the skin, enlargement of spleen and liver, hemorrhagic tendencies, anemia, leukopenia, thrombocytopenia, and roentgenological changes of the bones (mottled appearance and fusiform expansion of the lower third of the femur). The tentative diagnosis was confirmed by sternal bone marrow aspirations or punctures (Vogel, Rosenthal and Erf[12]). Splenectomy was performed on one of the patients because of mechanical obstructive symptoms, and on another in an attempt to overcome the symptomatic weakness and anemia. The bone marrows and the spleens from these patients were diffusely infiltrated with Gaucher cells, and were the sources from which the Gaucher cells were obtained for supravital study. The first investigators to study the cytological characteristics of the bone marrow in the first reported male having Gaucher's disease were Brill, Mandlebaum and Libman[3] in 1905.

Case Reports. CASE 1.—A. G. (359692), a white female, aged 32, was admitted to the Hematology Clinic, Out-Patient Department, on February 4, 1935, for confirmation of the clinical diagnosis that was established 15 years previously. At that time (December 27, 1920) the blood findings were: hemoglobin 60%; red blood cells 3,960,000; white blood cells 2000; platelets 64,000; neutrophils 56%; eosinophils 1%; lymphocytes 36%; monocytes 7%. The patient had a large spleen and a large liver. She complained chiefly of fatigue, weakness, swelling of ankles, and a feeling of oppression in the region of the stomach following meals. On the present admission, she complained of the same symptoms, although she had enjoyed fair health during the past 15 years. The family history was negative.

Physical Examination. The patient appeared pale and emaciated. She had a stunted stature and a barrel-shaped torso. She presented bilateral, lemon-colored pingueculæ, a few cervical lymph nodes, many brownish-purple spots on the lower extremities, and a spleen and liver that occupied 90% of the abdominal space. The spleen filled most of the left side of the abdominal cavity, while the liver filled much of the right. The blood pressure was 134/80.

Course. The patient had been receiving liver for a year in an attempt to raise the hemoglobin. This treatment was followed by some subjective improvement, but the blood findings varied little. The blood count at this admission was as follows: hemoglobin 64%; red blood cells 3,730,000; white blood cells 2050; platelets 60,000; neutrophils 54%; lymphocytes 44%; monocytes 2%. Roentgen ray examination of the long bones revealed a fusiform expansion of the lower third of both femurs. Because of the poor physical condition of the patient, a splenectomy to relieve the intraäbdominal pressure was not attempted.

Sternal Puncture. The sternal bone-marrow aspiration revealed the presence of Gaucher cells (both fixed and supravital preparations of the aspirated material were made). The marrow cell differential was normal (excluding the Gaucher cells); and a normal number of megakaryocytes were found.

CASE 2.—L. R. (282006), white female, aged 28, was admitted on July 9, 1935, for confirmation of the clinical diagnosis (established 8 years previously) and for splenectomy. On June 29, 1927, the blood findings were: Hemoglobin 80%; red blood cells 4,440,000; white blood cells 3400; platelets 80,000; neutrophils 68%; eosinophils 3%; lymphocytes 26%; and monocytes 3%. The complaints 8 years ago were fatigue, enlarging spleen, and nosebleeds. At the present admission, the complaints were increasing fatigue, increasing generalized purpura, increasing number of nosebleeds, and increasing pain in the region of the enlarged spleen. The blood findings on June 11, 1935 were: hemoglobin 74%; red blood cells 3,900,000; white blood cells 4600; platelets 80,000; non-segmented neutrophils 7%; segmented neutrophils 47%; eosinophils 5%; lymphocytes 37%; and monocytes 4%.

The family history revealed that the maternal grandmother had had an enlarged spleen. The mother, father, sister, and brother were all in good health.

Physical Examination. The physical examination disclosed a well-developed, pale individual with bilateral pingueculæ. The large spleen extended 8 cm. below the left costal margin. The liver extended 2 cm. below the right costal margin. The blood pressure was 98/60.

Roentgen ray pictures of the long bones revealed a fusiform expansion of the lower third of both femurs.

Sternal Puncture. Gaucher cells were present in the sternal marrow. The marrow differential counts were within normal limits when the Gaucher cells were excluded.

Course. Following splenectomy, which occurred on July 16, 1935, the usual platelets rise was found. On July 24, and August 3, 1935, the blood counts were respectively: hemoglobin 80 and 80%; red blood cells 4.96 and 4.8 million; white blood cells 26 and 13 thousand; platelets 420 and 700 thousand; non-segmented neutrophils 20 and 30%, segmented 60 and 53%; lymphocytes 11 and 12%; monocytes 9 and 5%. The patient made an uneventful recovery, and 6 months later exhibited much symptomatic improvement with the platelet count within normal limits.

Pathologic Anatomy. The spleen was 5 times the normal size. It had a pale, homogeneously red, smooth surface, and on cut section the same pale, red homogeneousness was exhibited throughout. Grossly, it had an "infiltrated" appearance, and microscopically it was diffusely infiltrated with Gaucher cells.

CASE 3.—P. S. (376602), a white male, aged 56, was admitted on February 5, 1935, seeking a diagnosis. His chief complaints were distress after meals, shortness of breath, swelling of the ankles, and an enlarging abdomen. These symptoms appeared during the 6 months preceding admission. The patient had not lost any weight, although he ate little because of the gas and distress that followed. The past history and the family history were negative.

Physical Examination. The physical examination revealed a pale, thin, emaciated individual with suggestive bilateral pingueculæ. The firm, smooth liver and spleen nearly filled the abdominal cavity.

Blood Findings. On February 5, 1935, the blood findings were: hemoglobin 59%; red blood cells 3,820,000; white blood cells, 1500; platelets 80,000; non-segmented neutrophils 10%, segmented 45%; myelocytes 7%; myeloblasts 2%; lymphocytes 35%; monocytes 1%; normoblasts 7 and megaloblasts 3 per 100 white blood cells. (Myelocytes and myeloblasts are rarely found in the peripheral blood stream in Gaucher's disease.)

Sternal Biopsy. A sternal bone-marrow biopsy confirmed the clinical diagnosis, and a splenectomy was done. Eight Gaucher's cells were found in every 100 nucleated cells of the marrow. There was no "shift to the left" in the marrow differential as might have been expected because of the presence of myeloblasts and myelocytes in the peripheral blood stream.

Course. The patient was much improved symptomatically 9 months after splenectomy.

Pathologic Anatomy. The same pictures as described in Case 2 were found.

CASE 4.—A. K. (389095), a white male, aged 62, was admitted on

January 21, 1936, complaining of chronic jaundice for 5 months and severe interscapular pains for 1 week. The family history and past history were negative.

Physical Examination. The patient was a fairly well developed, thin, moderately icteric male without pingueculæ, but with some mottled pigmentation of the skin on the legs. The liver extended 4 fingers below the right costal margin and was smooth and tender. The spleen was smooth and firm and extended 3 fingers below the left costal margin. The icterus index was 100; total blood proteins 5.6%; blood lipase, normal; hemoglobin 85%; red blood cells 4,660,000; white blood cells 5200; and platelets 60,000. The differential was: non-segmented neutrophils 7%, segmented 60%; eosinophils 2%; lymphocytes 29%, and monocytes 2%. There were 2% reticulocytes present. A Roentgen ray examination of the spine revealed a marked compression of practically all of the vertebral bodies.

Sternal Puncture and Biopsy. The aspirated sternal marrow contained many Gaucher cells. A sternal biopsy was done 2 days later, and again many Gaucher cells were found. The Gaucher cells were found to be in the same proportion in both the aspirated and biopsied marrow fluid, *i. e.*, they made up 11% of the marrow white cells.

Course. The patient improved after 4 weeks of rest in bed with an associated fall in the icterus index to 15 and was discharged.

CASE 5.—S. R. (386533), a white, 59-year-old clothier, was admitted to the hospital on November 8, 1935, complaining of progressively increasing pains in the right knee following an injury to his right leg 7 weeks previously.

Physical Examination. The patient was a well developed, slender man with exquisite tenderness over the right hip. The right leg was maintained in a semiflexed position. The spleen was not palpable; neither was the liver. Pigmented discolorations were present on the anterior aspect of both legs.

Laboratory Findings. Hemoglobin 82%; white blood cells 8200; platelets 140,000; non-segmented neutrophils 2%, segmented 78%; lymphocytes 20%. A Roentgen ray examination of the chest revealed a slightly elevated diaphragm on the left side. Roentgenologically, there were areas of absorption in the right femur and throughout the pelvis. There was also evidence of osteoarthritis of both hips. The process was considered to be one of metastatic malignancy, and the patient received deep radiotherapy.

Sternal Puncture. A sternal bone-marrow puncture revealed the presence of Gaucher's cells. These comprised 15% of the nucleated marrow cells.

This was a most unusual case of Gaucher's disease, since neither the liver nor the spleen were palpably enlarged.

Staining Characteristics of Gaucher Cells. With the Jenner-Giemsa stain, Gaucher cells appear as large, light gray staining, wrinkled cells, often mutinucleated. The endothelial-like nucleus is usually crowded eccentrically because of the Gaucher substance which accumulates in the cytoplasm as fibrils. These fibrils are not stained by osmic acid nor Sudan III, and reveal no crystals by polarized light. Many of the cells appear to be vacuolated and therefore are known as "foam" cells. However, we have found these cells are not vacuolated. With special stains Kettle[5] was able to stain mitochondria in the young single-nucleated cells.

Supravital Characteristics of Gaucher Cells. *Cytoplasm.* The supravital technique used in this study was that devised by Sabin.[10]

Gaucher cells vary in size, depending on their age (Fig. 1). The young cells resemble reticulum cells or young monocytes. The cloudy, hazy, yellowish cytoplasm contains a few small, irregular, threadlike mitochondria and a few (1 to 10) Gaucher fibrils. As the cell becomes older and larger, due to the increased accumulation of fibrils, the cytoplasm becomes grayish white and the mitochondria disappear. No mitochondria are seen in cells having a diameter of 35 microns or over. In old multinucleated cells the cytoplasm becomes granular. Masses of old cytoplasm without nuclei are seen occasionally.

Fibrils. The fibrils are often curved or "S" shaped with tapered extremities. They measure 5 to 10 microns in length and from a half to 1 micron in width at the widest diameter. Those found in young Gaucher cells occasionally assume a deep maroon color with the neutral red of the supravital stain. This observation was rather infrequent and was probably due to a local concentration of neutral red stain upon the slide. The fibrils of the older cells usually lie in parallel lines and never extend from one cell into another.

Nuclei. The nuclei are very similar to those of endothelial cells. They are relatively small, with blotchy chromatin, a thick nuclear membrane, and an occasional nucleolus. The young Gaucher cells contain only one centrally located nucleus, while the older cells are often multinucleated with the nuclei dispersed at random throughout the cytoplasm. It has been reported that as many as 22 nuclei have been seen in one cell. With the supravital technique, no cell has been seen that contained more than 7 nuclei.

Granules and Vacuoles. In supravital preparations vacuoles are rarely seen in Gaucher cells. However, many spheroid translucent cytoplasmic granules are seen which vary in size and number. They have a yellowish tint, and a solid hyaline structure and are scattered between the Gaucher fibrils. In stained preparations, however, vacuoles are frequent, and no intracellular granules are present. Marchand and Risel both noted this discrepancy (using fresh tissue films) and stated that the vacuoles appeared after the cells had been treated with alcohol, acetone, chloroform or xylol. They assumed that the refractile granules seen in the fresh unstained preparations were alcohol soluble. When alcohol was placed under coverslip of a supravital preparation while cells containing these granules were in focus under the microscope, an occasional peripherally situated granule would escape the confines of the cell. However, the vast majority of the granules did not escape. Perhaps the cell membrane protected the granules to some extent. At least, the alcohol solubility of these granules did not completely explain the discrepancy between the presence of the vacuoles in the stained preparation and the presence of the granules in the supravital preparations. Bohrod[2] recently described a similar discrepancy in the cells of a case of atypical myeloid leukemia.

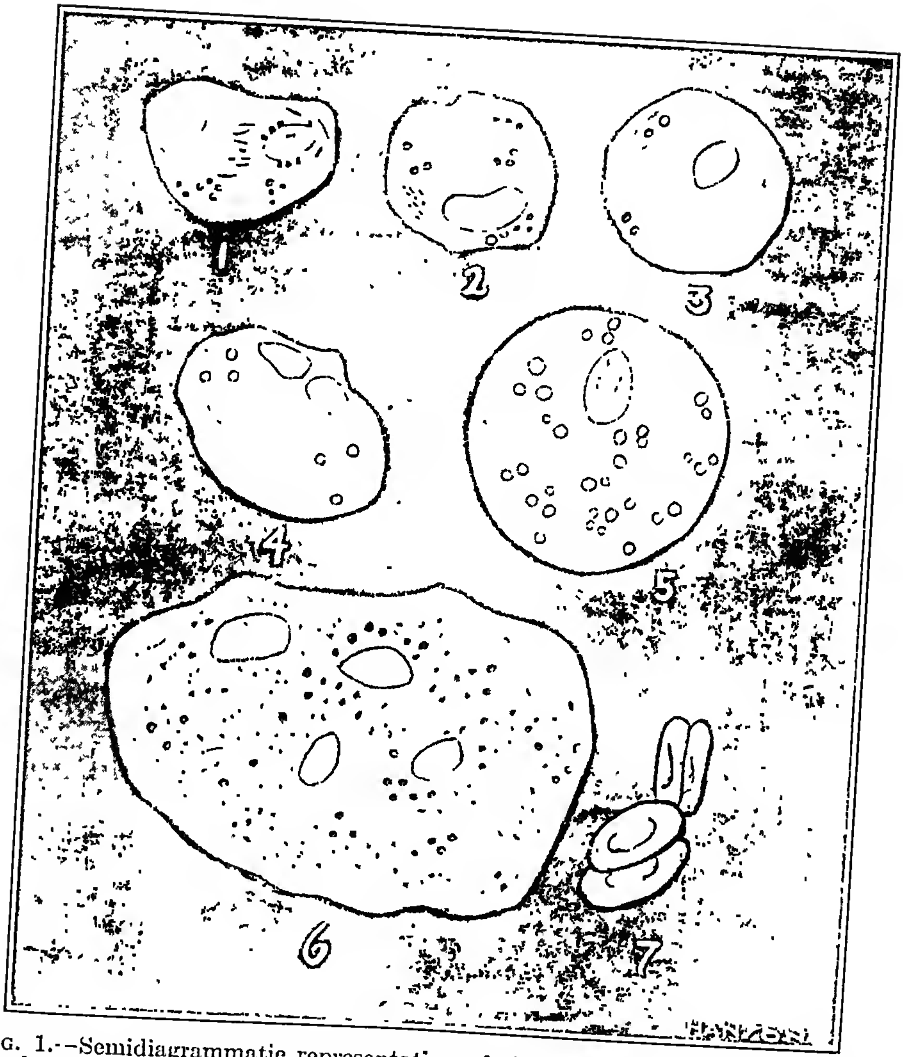

FIG. 1.—Semidiagrammatic representation of single Gaucher cells. 1, 2, and 3, Young Gaucher cells. 4 and 5, Intermediate stage exhibiting the translucent bodies 6, Old multinucleated Gaucher cell. 7, Red blood cells.

Many of the myelocytes and eosinophils in his case, contained peculiar inclusions or granules when studied in wet preparations while only vacuoles were found in the stained preparations. After considerable study, he concluded that the inclusions or granules had a refractive index similar to oil or balsam since the granules could be seen in the stained smears if the high dry lens was used; whereas only vacuoles could be distinguished when the oil-immersion lens was used. We were fortunate to have a case of the same atypical type of myeloid leukemia and were able to verify Bohrod's findings. We then applied his findings to the Gaucher cell granules, which were similar (to the atypical myeloid granulations), and discovered that the Gaucher cell granules could be seen in stained preparations if the high dry lens was used.

Similar granules were described in the leukocytes of 3 cases of ichthyosis by Sabolotny.[11] It appears that these granules or bodies occur in many different disease processes. Unfortunately, they cannot be stained by any of the dyes that are in common use.

Motility. Gaucher cells have no gross motility in the supravital preparations. However, the cytoplasm of most of the young cells is fluid, for the mitochondria, the fibrils, and the hyaline refractile granules move quite freely in the cytoplasm. Motility of the fibrils is impossible in the older cells since the fibrils are compressed by their accumulation.

Origin of Gaucher Cells. The origin of Gaucher cells is not definitely known. Mandlebaum and Downey[7] and Kettle[5] state that Gaucher cells probably arise from the reticulum cells. The supravital appearance of the young Gaucher cells favors this opinion since they are morphologically and characteristically similar to reticulum cells.

Because of the disturbed lipoid metabolism in Gaucher's disease, Doan and Wiseman[4] suggested that a lipoid might be the stimulus provoking the formation of Gaucher cells from the reticulum. In this study only the Gaucher cells or reticulum cells contained fibrils and hyaline granules. These structures cannot be found in other marrow cells. This would indicate that the process attacks only the reticulum cells as such and not their descendants. Bloem, Groen, and Postma[1] have shown that the total blood fats, blood cholesterol and blood lecithin are within normal limits but that the lipoid nitrogen is increased in Gaucher's disease.

Summary. 1. Five cases of Gaucher's disease are presented; 3 had unusual associated findings. One showed myelocytes and myeloblasts in the peripheral blood stream; the second had no palpable enlargement of the liver or spleen; and the third was severely jaundiced.

2. The supravital staining characteristics of Gaucher cells are described.

3. Many of the Gaucher cells after fixing and staining, in addition to the fibrils, contain vacuoles or "foam." The latter are probably intracellular bodies.

We wish to express our appreciation to Dr. N. Rosenthal for much valuable aid.

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OBSERVATIONS ON SEVENTY-EIGHT CASES OF PERNICIOUS ANEMIA WITH SPECIAL REFERENCE TO WEIGHT CHANGES.

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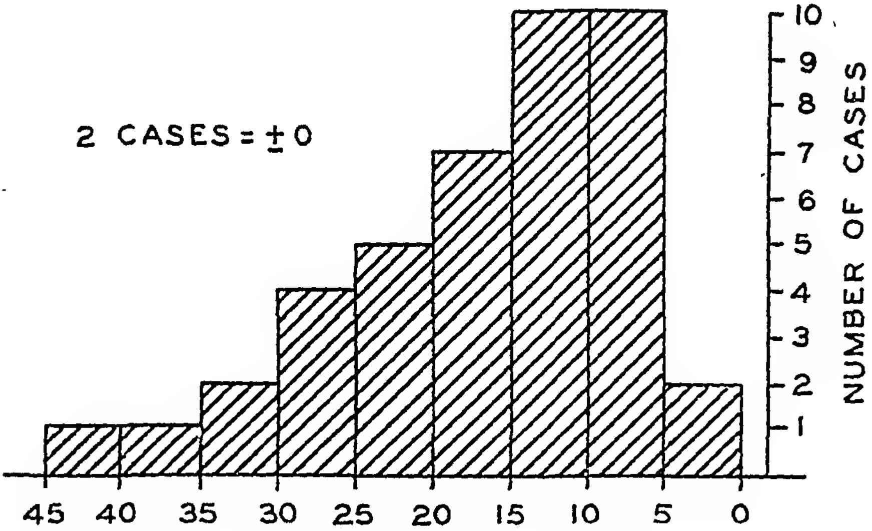
Addison wrote in the first description of pernicious anemia in 1855, these words: ". . . nevertheless, to the very last and after a sickness of several months' duration the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect."

This concept that patients with pernicious anemia show little, if any, loss of weight has been generally accepted since that time. Although several of the current text books of medicine[1,2,12] state that considerable loss of weight may be found in the occasional patient, the distinct impression is gained both from these and other sources that significant weight loss in pernicious anemia is rare. Because of a contrary impression gained from observing a number of patients from the Mid-South with pernicious anemia it seemed worthwhile to analyze the records with regard to this point. Other findings, aside from weight changes, which appeared to be of interest will be mentioned briefly.

Material. Records of 88 patients with pernicious anemia were available in the Vanderbilt University Hospital files; 45 of these were found to be suitable for a study pertaining to weight changes. The remainder were rejected for the following reasons: in 19 some doubt was entertained regarding the correctness of the diagnosis; 6 patients had been correctly diagnosed and treated prior to admission to this hospital, but their records contained insufficient data with regard to weight; 2 patients had been treated here, whose records lacked sufficient weight data; and 17 patients had complicating diseases which interfered with the interpretation of weight changes. In the latter group there were patients with pernicious anemia and congestive heart failure, diabetes mellitus, edema due to venous obstructions, and so on.

TABLE 1.



Percentage Deviation of Admission Wt. from Usual Wt. (Uncomplicated).

TABLE 2.—DIFFERENCE OF MATHEMATICAL SIGNIFICANCE BETWEEN THE MEANS OF THE "USUAL" AND "ADMISSION" WEIGHTS, AND BETWEEN THE MEANS OF THE "ADMISSION" WEIGHTS AND "IDEAL" WEIGHTS, BUT NO SIGNIFICANT DIFFERENCE BETWEEN THE MEANS OF "IDEAL" AND "USUAL" WEIGHTS.

(In Order for a Difference Between Means to be Significant this Difference Must Equal or Exceed 2 Times the Standard Error of this Difference.)

Mean of ideal weights . . .	152.1	Mean of ideal weights . .	152.10
Mean of usual weights . .	150 0	Mean of admission weights	124.93
Difference	2.1	Difference	27.17
S. E. of difference	5.02	S. E. of difference . . .	4.73
∴ This difference is not significant		∴ This difference is significant	

Mean of usual weights . . .	150.00
Mean of admission weights .	124.93
Difference	25.07
S. E. of difference	5.85
∴ This difference is significant.	

Of the 69 patients in whom the diagnosis appeared to be clearly established there were 43 males and 26 females, with ages ranging from 22 to 81 years. The duration of symptoms varied from 3 weeks to 10 years. Signs or symptoms of spinal cord involvement were present in 51 members of this series. Of this number 18 had paresthesias only; 33 presented objective signs of spinal cord damage. The admission red blood cell counts ranged from 550,000 to 4,400,000. Five Negroes were included in the group. Serum proteins were determined on 14 patients. Values below normal for either the total serum proteins or for albumin or globulin were found in 13 instances.

Procedure. The 45 records which form the basis of this study concerning weight changes included both hospital and outpatient admissions, although the great majority had been treated in the hospital. Wherever possible the "usual" weights of the patients were determined from the histories. All patients were weighed as part of their admission examination. The "ideal" weight estimates were based on the tables by Davenport.[6] "Usual" weights, of course, were those given by the patient and are admittedly open to question, as are all data so derived.

It is of interest to note that in the clinical descriptions of these patients the term "emaciated" was applied 9 times; 12 patients were classed as undernourished or poorly nourished; 6 were described by some other term suggesting loss of weight; 12 were described as being well nourished or fairly well nourished; 1 was called obese, and there was no relevant comment in 6.

Inasmuch as the records did not permit the listing of each of the 3 weights for every patient, the number of items in the various weight groups is not the same. From these 3 sets of weights, percentage deviations of the usual weight from the ideal weight, the admission weight from the ideal weight, and the admission weight from the usual weight, were calculated (Table 1).

The means of the 3 weight groups were determined and these means subjected to mathematical analyses in order to determine whether there is any difference of mathematical significance between these means (Table 2). It is thus shown that there is a difference of mathematical significance between the means of the "usual" and "admission" weights, and between the means of the "admission" and the "ideal" weights, but no significant difference between the means of the "ideal" weights and the means of the "usual" weights.

An attempt was made to correlate the degree of weight loss with other factors, such as the duration of symptoms and the level of the red blood cell count found on admission. There was no apparent correlation between these factors.

Of the 43 patients who had lost weight at the time of admission 28 gained weight after the institution of specific therapy. However, recorded weights after the beginning of treatment were at such extremely variable intervals that it was impossible to follow rates of gain in given periods, or indeed, in some instances due to omissions, to determine whether any change in weight had taken place. A number of the patients who showed no gain in weight were followed for too short a time to justify any statement with regard to this point. Of 32 patients whose weight was followed for 3 weeks or more after the beginning of treatment all but 3 showed a gain in weight. These gains ranged from 2 to 53 pounds. There appeared to be some correlation between the amount of weight gained and the elapsed time after beginning of treatment, but the extremely irregular intervals at which follow-up weights were recorded makes this uncertain. There were, however, several patients showing marked gains of weight within a relatively short time. For example, 7 patients over periods not exceeding 16 weeks gained 20, 16, 20, 53, 34, 16, and 21 pounds, respectively. The weights of 9 patients were not followed. Loss of weight during treatment was recorded for 2 patients who had been followed for as long as 3 weeks. No change in weight was noted for 4 patients after treatment.

Discussion. This study indicates that weight loss occurs almost always in pernicious anemia and that weight gain is to be expected after the institution of treatment with liver extract. Several suggestions come to mind concerning possible causes for the changes in weight noted. It might be said that these patients are mostly in the middle and elderly age groups when loss of weight is common and due, presumably, to associated vascular changes. Against this idea is the fact that the majority of such patients gained weight after the use of liver or liver extract. Diarrhea and vomiting occurred in a considerable number of patients, but was usually transient and probably was not a major factor in the causation of weight loss. The fact that in certain patients seen in the outpatient department a gain in weight followed the administration of liver extract (usually intramuscularly) even though no change in the diet was made would lead to the suggestion that this weight loss was due, in part at least, to a deficiency in some factor contained in liver extract. Of course, as the patient's blood responds to the hemopoietic factor contained in liver he feels better generally and is likely to regain his appetite. However, it is a frequent clinical observation that a feeling of marked improvement occurs within a short time following the administration of liver extract, this occurring days before there is any appreciable increase in the red blood cell count. Liver extract is known to contain both vitamin B_1 and B_2[10] in considerable amount, and the relation of vitamin B_1 to appetite, gastric secretion and intestinal tone has been demonstrated.[4,5,7,11] Other work[8,9,13] has shown that there is contained also in liver another factor or factors which has a marked growth-stimulating effect in experimental animals and that this factor (or factors) is entirely independent of the vitamin B content of liver. Thus it would seem that factors other than those solely concerned with hemopoiesis may possibly play a part in the causation of the changes in weight observed.

Inasmuch as various deficiency states are known to exist in the United States, the possible deficiency of the extrinsic, or food, factor in these patients must be considered. Youmans and his associates[14,15] have shown that nutritional edema is a fairly frequent finding in the Mid-South and it is of interest to note that of the 14 patients in whom the serum proteins were determined all but one showed what were regarded as abnormally low values. Cornell[3] in 1927 analyzed the pre-anemia diets of 26 patients with pernicious anemia over a period of 10 years and found that there was apparently no significant difference between the diets of these people and their associates who remained free from this disease. While we have no such data concerning our patients we have no reason to believe that their disease has not resulted from a lack of the intrinsic factor of Castle which is the usual cause of pernicious anemia.

Summary. 1. Of 44 patients with pernicious anemia, 42 showed a loss from their usual weights on admission to this hospital. These losses ranged from 2% to 42%. It was shown that there was a difference of mathematical significance between the means of the the "usual" and "admission" weights; and between the means of the "admission" and the "ideal" weights, but no significant difference between the means of the "ideal" weights and the means of the "usual" weights.

2. Gains in weight were recorded for 28 members of this series following the institution of specific therapy. The follow-up weights were taken at too varying intervals to permit us to say that other patients would not have shown a gain in weight, had their weights been recorded.

3. It is suggested that there may be a factor or factors present in liver extract, aside from the hemopoietic principle, which may play a part in the weight changes recorded.

4. These findings are to be regarded as typical for the Mid-South. A comparison with similar data from other sections of the country would be interesting.

I wish to express appreciation to Dr. C. S. Robinson of the Department of Biochemistry and to Mr. L. L. Chastain of the Department of Physiology, Vanderbilt University School of Medicine, for aid in the preparation of the mathematical data and to Dr. P. J. Fouts of Indianapolis, Indiana, for information concerning the vitamin content of liver and liver extract.

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RUBBER SHEATHS AS VENEREAL DISEASE PROPHYLACTICS:

THE RELATION OF QUALITY AND TECHNIQUE TO THEIR EFFECTIVENESS.

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IN venereal disease prophylaxis, the sheath is accorded a high usefulness against both syphilis and gonorrhea. In contrast, the value of the ordinary sanitube may be restricted to the prevention of syphilis; against gonorrhea, the male patient should employ further measures.[6] Harrison[4] writes "A condom is the most efficient safeguard so far as the parts which it covers are concerned, and these are the most frequent sites of infection." Scherber[8] mentions the importance of the sheath as a prophylactic for both male and female. Gelatte[3] recommended the addition of the sheath to the naval sanitube packet. Pelouze[7] states "Next to continence, the use of the condom is probably the safest prophylactic measure, but this, carelessly used, is far from absolute." Brunet[2] quotes the resolution of the All America Conference on Venereal Diseases (adopted only by the Section on Diagnosis and Treatment of Syphilis), which reads in part as follows: "The most efficient measure probably is the use of a mechanical device that prevents actual contact." More recently, Millspaugh[5] has written "At present, though not ideal, the condom is at once the most widely used and safest prophylactic. It is the nearest approach to a universal veneral prophylaxis." The success achieved in reducing the venereal rate among American troops in China[1] in 1930 has been partially attributed by Gelatte[3] to the enforced use of the sheath.

In view of the common dependence of the physician upon the rubber sheath in venereal disease prophylaxis, it is in order to record the beginnings of a critical analysis of the quality of American rubber sheaths.

Only an understanding of the commercial background can make clear the reasons for the inferior quality of rubber sheaths as they are sold to the public. Two concerns produce more than 50%, and 5 concerns manufacture approximately 90% of the estimated yearly volume of 317,000,000 individual sheaths having a retail-value of perhaps $25,000,000.

Within the past 7 years manufacturing methods have undergone radical change, eliminating the old fashioned "cold chloride cure" for sheaths dipped from crepe rubber dispersed in a solvent such as benzene, in favor of a new "hot cure" or vulcanization, for sheaths dipped from an improved solution itself containing the vulcanizing ingredients. Even more drastic has been the shift from dipping solutions of crepe rubber to liquid latex, which is a suspension of clean rubber sap in water, for liquid latex has proved more adaptable to automatic manufacturing processes which have greatly lessened production costs. Only the third largest manufacturer now dips from crepe rubber solutions, and even this manufacturer operates a completely automatic latex machine with a capacity of about 175,000 sheaths per 24-hour day.

Improvements in testing have not kept pace with those in production, so that testing remains a skilled hand and eye operation, infrequently supplemented by a compressed air jet for inflation. However, a large part of the output of this industry is never tested from the time the sheaths are stripped from the dipping formers to the moment of use by the consumer. Moreover, there is ample evidence of the existence of a wholesale and jobbing market for sheaths which have been tested and found defective. Most sheaths are quickly and cheaply tested; only 3 or 4 of the many better known brands are carefully tested, and these are not 100% perfect.

The manufacturers sell to the drug wholesalers and to wholesalers of sheaths. The sales of the former are largely confined to the drug trade; the latter have developed all possible retail outlets in order to increase sales volume. The unwillingness of the retail druggist to be content with a liberal (say 100%) mark-up on his purchase price has sharply limited consumer demand for drug store sheaths and has strengthened the sales by jobbers to improper purveyors, such as street and office peddlers, gasoline stations, cafes and restaurants, barber shops, cigar stands, newsstands, porters, bootblacks, and the like. Unable to move a sufficient volume through drug channels, manufacturers have encouraged the persistence of their own wholesalers and jobbers selling to all manner of retail outlets. In contrast with a production cost often below 50 cents per gross, retail prices to the consumer average $16.00 per gross (3 for 35 cents) in drug stores, and $12.00 per gross (3 for 25 cents) in other retail outlets. The retail profit margins on this type of merchandise are uncommonly high and the demand constant.

The retail drug stores sell about one-third of all the sheaths sold; their higher prices probably yield them about 45% of the estimated aggregate retail dollar volume of $25,000,000 per year.

Results of Tests Conducted by Voge. In 1934 and 1935, C. I. B. Voge tested somewhat more than 2000 American rubber sheaths. These were purchased largely in the open market, but several brands were purchased from manufacturers themselves, and two of the brands were donated as samples by their manufacturers. These last two are not among the best brands according to the Voge tests. Purchases were made with the object of securing a wide sampling and one which would be roughly representative of the market as then known. Table 1 gives the results of the tests.*

TABLE 1.—RESULTS OF VOGE TESTS.

		Perfect.		Pinholes.**		Burst.		Flaws.†	
Brand. (1).	Total number tested. (2).	No. (3).	Per cent. (4).	No. (5).	Per cent. (6).	No. (7).	Per cent. (8).	No. (9).	Per cent. (10).
1	74	70	94.5	1	1.4	1	1.4	2	2.7
2	74	64	86.5	2	2.7	5	6.8	3	4.0
3	80	61	76.3	1	1.3	5	6.3	13	16.2
4	144	109	75.6	3	2.1	6	4.2	26	18.1
5	146	108	74.0	6	4.1	18	12.3	14	9.6
6	60	42	70.0	6	10.0	3	5.0	9	15.0
7	78	42	53.8	4	5.1	11	14.1	21	27.0
8	60	29	48.3	11	18.4	1	1.7	19	31.7
9	182	89	48.9	31	17.0	44	24.2	18	9.9
10	216	91	42.1	12	5.6	12	5.6	101	46.7
11	74	29	39.2	8	10.8	18	24.3	19	25.7
12	72	26	36.1	12	16.7	5	6.9	29	40.0
13	74	25	33.8	3	4.1	2	2.7	44	59.5
14	108	35	32.4	14	13.0	11	10.2	48	44.4
15	75	21	28.0	16	21.3	23	30.6	15	20.0
16	74	14	18.9	13	17.6	3	4.1	44	59.5
17	216	22	10.2	77	35.6	104	48.2	13	6.0
18	146	13	8.9	66	45.2	61	41.7	6	4.1
19	72	6	8.3	13	18.0	47	65.3	6	8.3
20	50	0	0.0	..	....	50	100.0	..	....
21	74	0	0.0	32	43.3	42	56.7	..	....
Totals	2149	896		331		472		450	
Weighted averages . .			41.7		15.4		21.9		20.9
Adjusted weighted averages			40.9		15.2		29.4		14.5

** Pinholes surviving inflation.
† Other flaws surviving inflation.

The test employed by Voge has been described as a prolonged inflation test and was devised primarily to reduce the factor of human error in examining rubber sheaths for flaws, especially pinholes. Essentially the technique consists in inflating each sheath to a moderate size, an ellipsoid about 8 inches long and 6 inches in diameter, clipping to close the open end, and then either hanging it from the ceiling, on racks, or placing it on continuous belts. In either case each sheath remains inflated for at least 15 to 20 minutes and in this time any holes will produce marked deflation and thus facilitate their detection. Those which retain their original volume of air are then visually examined against an illuminated ground glass background. Careful examination reveals flaws other than holes: dirt specks and foreign matter, creases or overlapping folds, blisters, thin spots, weak tips, very uneven dipping. Sheaths exhibiting these defects are recorded in Column 9. Those which burst with this degree of inflation are also classed as defective and are listed separately in Column 7. The theory underlying the classification of bursting as a defect is that a rubber sheath which cannot withstand this moderate inflation cannot be tested adequately and must, therefore, be assumed to be defective. It is not yet possible to set a standard of volume for inflation because the clinical significance of capacity for inflation is unknown. Since those with pinholes were not reëxamined against the illuminated background, it is not possible to say how many may have had additional flaws. It must be further borne in mind that, since the sheaths were first inflated, those which burst may have had pinholes and other flaws. Hence both pinholes and other flaws are somewhat underestimated for the present sample.

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* The names of the Brands tested in this study will be furnished on application to the authors.

To what extent may the present sampling be taken as representative of the entire United States market? The quantities tested are admittedly small and hence not highly reliable from the point of view of their adequacy. Further, the quantity tested of each brand was not rigidly set in pursuance of a weighting plan according to each brand its relative importance on the market. Finally, the knowledge of the internal organization of the commercial market was less complete at the time of selecting the sample than it subsequently became. With these factors in mind, a simple weighted average was computed for each column. In order to check the validity of the resulting averages from the standpoint of the representativeness of the data (not their adequacy), and on the basis of an improved knowledge of the internal organization of the market, a system of weights was devised and applied in turn to each per cent column in order to calculate for each category (passed, pinholes, burst, and other flaws) the number of sheaths which would be expected in a completely representative sample of 1000. The results, reduced to percentages, appear in Table 1 as adjusted weighted averages.

Critical Analysis of the Prolonged Inflation Test and Proposed Laboratory Tests to Furnish More Exact Information. It is apparent that the Voge technique is an arbitrary one. There are no clinical data indicating what per cent of the sheaths with each type of flaw for which rejection was made might be expected to fail under conditions of actual use by the patient. The test had, perforce, to be a practical one, and was evolved from existing commercial tests of the rule-of-thumb type. However, one statement can be made: that any hole or tear in a rubber sheath renders it unfit for use as a prophylactic. All flaws other than holes are considered important to the extent that they may result in holes or tears in actual use. Here, again, it is important to keep in mind that no quantitative data exist, and it is not possible to say what per cent of the sheaths containing any given defect will fail in use.

It is known that overlapping folds and uneven dipping result in a maldistribution of stress when a strain is put upon the sheath and that this condition is likely to be associated with a tear.

Similarly, a thin spot caused by the failure of one or more dips adequately to cover the entire surface of the dipping former represents a section of rubber weaker than the surrounding area. Less resistant to strain, this section is a possible basis for a hole or tear.

Weak tips may result when a freshly dipped former is turned up so as to permit the fluid to run down the former, especially when this is done either too long or too soon. Gravity pulls the fluid away from the tip. When dry, this section is weakest and inflates first. Since the tip is the site of the greatest strain, such a condition is thought to warrant rejection.

Dirt and other foreign matter are dangerous when present in clearly visible size, although the exact size to be set as the borderline between safety and danger cannot be determined at the present stage of research. Particles of dirt and foreign matter are easily loosened from position in the wall of the sheath, thus leaving a hole or starting a tear.

Blisters, like thin spots, are areas where there has been but one dip in the case of double-dipped sheaths. The blister results when a bubble of gas breaks through the outer film and leaves a crater-like portion of the wall with relatively thick rim and exceedingly thin center. The thin center often becomes a hole upon being stretched.

Inflation occupies an ambiguous place in the testing technique. Some elements in the industry appear to assume that a given amount of inflation can be correlated with results obtained in use, although there are no data to support this view, and although all recorded inflation tests have at best taken into account only one factor, namely volume, to the exclusion of pressure and temperature. Inflation, does, however, have utility and is indispensable at the present time. The relative importance of certain flaws or defects, such as those discussed above, can be allotted and a classification described and agreed upon. The problem then becomes one of discovering the defects. Inflation is at present the only means of, finding those characteristics which have here been tentatively designated flaws. In general, the greater the inflation, the more readily defects are observed. Extreme inflation of the modern soft cured sheath induces a permanent set which tends to make the sheath unfit for use. *A cubic volume of one-third of a foot is suggested as a tentative standard for testing by inflation.* The shape assumed by various sheaths when inflated makes it difficult to give corresponding specifications for length and diameter, but one-third of a cubic foot would be represented by a cylinder roughly 8 inches in diameter and 11 inches in length or altitude.

Other elementary testing techniques have been applied by manufacturers who seek processing controls. For the most part, these are simple weight and space measurements, aging tests or tensile strength tests. Of these the least significant has been tensile strength determination on longitudinal and lateral sections, and the reason is that no real investigation appears to have been done on this important property. Space measurements by manufacturers have included wall thickness.

There would seem to be a need for more exact laboratory examination of the elementary physical properties of rubber sheaths. Strength and elasticity should be explored along the following lines: elongation and reduction in area; softness or hardness; yield point, elastic limit and ultimate strength, together with permanent set measured as a percentage increase in length and width; full detail on stress/strain characteristics. More detailed work on the rôle of grain and fiber in tensile strength would be valuable. Microphotographs have been too little used and studied. A mechanical fatigue test would add useful knowledge about sheaths. The physical chemistry of hardness (or softness) may give some clue to conductivity. Finally, data on resistance to abrasion would permit a more intelligent description, classification and evaluation of rubber sheaths than the present limitations upon knowledge permit.

The Practical Results of the Present Situation for the Physician. Is, then, the physician, in view of these criticisms of faulty material and testing, to abandon mechanical devices and advise his patients not to rely on mechanical prophylaxis? Such a conclusion would appear extreme, and it is suggested that the present limitations on the usefulness of the rubber prophylactic can be largely overcome by the following procedures: first, more careful purchasing; second, more thorough instruction of the patient in the technique of using and testing the rubber sheath; and third, throwing all possible influence behind a demand for adequate regulation of the quality of sheaths at their manufacturing source.

Selective purchasing would be simple if the results of present tests could demonstrate incontrovertibly that, say, 1, 2, 3, and 4 are the best brands and are safe to use. The Voge tests, although useful as indications, do not meet this need, and the results are of tentative value. A selection of reliable brands is possible, and such results can be of value. It is also to be remembered that purchases should be made only from reputable wholesale and retail druggists.

In order to obtain the greatest protection from the mechanical prophylactic the patient should be instructed in methods of testing, in rolling and preparing for use, in placing, in removal and in aftercare. That the patient has a satisfactory familiarity with the sheath should not be lightly assumed; advice on purchasing is especially worth while.

Two methods of testing are recommended for the patient: inflation with air and filling with water. Lengthwise or lateral stretching alone is almost useless. Inflation with air to a shape about 11 inches long and 8 inches across permits careful visual examination, but to be effective this must be conducted under good lighting conditions. The best light source is one which is strong but evenly diffused. The sheath should be placed between the observer and the light source. Those with heavy tips require separate inflation of the tips. To inflate the tip one grasps the sheath loosely in both hands in such a manner that the open ring rests on thumb and forefinger of one hand and the body of the sheath hangs vertically within the closed fingers of each hand. In this position one partially closed fist rests above the other; air is introduced at the open end of the sheath, and only the tip is free to inflate. Perhaps a simpler way is to roll the sheath half way and then to inflate. If the observer turns the inflated sheath about before sensitive areas on the face, pinholes are more easily located than is possible with the untrained eye alone.

With the liquid latex product and the improved methods of compounding crepe rubber solutions, the problem of the age of the rubber prophylactic has almost disappeared. Rubber sheaths now commonly have a shelf life of two or more years.

Rolling is easily learned. The unrolled sheath (preferable to the rolled) is drawn smooth on two fingers of one hand so that the ring is at the knuckles and the closed end hangs down from the finger tips. Two fingers of the other hand can then gently and evenly roll the sheath toward the finger tips. Four or five strokes quickly produce a rolled prophylactic ready for use.

Certain refinements in the technique of using the sheath contribute to its usefulness as a prophylactic by increasing efficiency and by lowering psychic objection on the part of the patient. Active coital movement following ejaculation increases the likelihood of leakage of infected semen from the open end of the sheath as detumescence takes place. Similarly, withdrawal after detumescence is well advanced incurs the risk of spilling the contents in the vagina or on the vulva and the risk of contact between the penis and infected areas. If the ring of the sheath is felt and held to the root of the male organ at the moment of withdrawal, the danger of its slipping off is minimized. Some authorities deny the necessity for leaving a free half inch at the tip of the sheath for the ejaculate, but in patients complaining of discomfort at ejaculation, it is found that the presence of a pocket or space at the tip of the prophylactic may remove the cause of dissatisfaction and thus increase the probability that the patient will protect himself. In order to leave a space at the tip, the patient should be instructed to void the air from a half inch at the very tip by twisting it and holding it thus while unrolling the sheath on the erect penis so that no air will be imprisoned in the sheath.

The diminished sensation and the not infrequent lessening of satisfaction accompanying the use of the sheath cannot be entirely overcome, but some men report less interference with normal sensation when the glans penis is lubricated just before the sheath is placed. The objection of the female partner to the sheath is seldom likely to be emphatic; intelligent questioning can be expected to reveal inadequate lubrication or some other fault of technique in most cases.

Some writers[5] warn against intromission before placing the sheath, and the necessity for this precaution seems entirely clear.

In removing the sheath, care must be taken that none of the material on it contaminates. Millspaugh[5] writes "The condom should be carefully removed as a glove is stripped from the hand to avoid contact with the contaminated external surface." Since the act of removal creates a possibility of infection, and in view of the fact that the sheath "fails at the root of the penis and the pubis" Harrison[4] suggests that disinfection follow the use of the sheath. This seems excellent advice, and practical in view of the reliability of soap and water.[7]

Inadequate lubrication causes many preventable tears. All patients using mechanical methods should be warned to assure themselves of adequate lubrication, either naturally or artificially provided, before intromission. Where supplementary lubrication is desired, a water dispersible lubricating jelly is somewhat preferable to any of the fatty lubricants. Should a break occur, the patient will need chemical means of protection and should be warned to prepare for emergencies, the immediate use of soap and water being thought of first.

In conclusion, the writers believe that the physician can perform a public service by supporting or originating attempts to improve and to control the quality of mechanical prophylactics at their source. The responsibilities and importance of this industry from the point of view of public health rest but lightly upon the shoulders of its controlling elements, who fail in public spirit and social outlook. Clearly the public health requires prompt, thoroughgoing action to provide more reliable mechanical prophylactics.

Conclusions. 1. Recent changes in manufacturing processes have markedly improved the durability of rubber sheaths which also present increased possibilities for dependability and high quality if manufacturers and distributors will apply adequate tests and will scrap defective sheaths.

2. It is in the physician's province to furnish such guidance in purchasing and such instruction in testing and use as will assure the patient a high degree of reliability.

3. Dependability cannot be expected from random purchases of rubber prophylactics, however, since only about 40 ± 5% of the rubber sheaths sold in the United States are thought by the authors to be fit for use.

4. The reasons for the prevalence of inferior rubber sheaths are economic in origin, and operate through discouraging careful testing on the part of the manufacturer or wholesaler marketing his own brands.

5. In order to permit more accurate judgment on the reliability of specific commercial brands, present rather rudimentary methods of evaluation require further elaboration.

6. The commercial factors, combined with the user's ignorance of the necessity for making his own test, give the rubber sheath a prophylactic usefulness far below the value which could be established by control of quality through adequate testing.

* The authors are indebted to Dr. Clarence J. Gamble for his assistance in the preparation of the material for publication.

When this article was written, the State of Oregon had just pioneered with a state law empowering the Board of Pharmacy to set and to enforce standards for both chemical and mechanical prophylactics. More recently, legislation of similar import has been passed in Idaho and in California. Under date of October 4, 1937, the Food and Drug Administration notified manufacturers and dealers in venereal prophylactics that "Regardless of the nature of the products, or methods by which they are used, all articles intended as venereal disease preventives are subject to the provisions of the act (Federal Food and Drugs Act)." The authors welcome these important steps in the direction of the quality control they believe to be essential.

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CLINICAL EXPERIENCE WITH SULPHANILAMIDE IN THE TREATMENT OF BETA HEMOLYTIC STREPTOCOCCIC INFECTIONS.*

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Since the report of Domagk,[7] which pointed out the specific chemotherapeutic action of derivatives of para-amino-benzene-sulphonamide in experimental beta-hemolytic streptococcic infections, there have been numerous articles in the literature dealing with experimental and clinical aspects of their use. The work of Buttle, Gray and Stephenson,[2] Colebrook, Buttle and O'Meara,[4] Fuller,[10]

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* This study was made possible by a grant from the Clinical Research and Teaching Fund, Yale School of Medicine.

TABLE 1.—CASES OF ERYSIPELAS TREATED WITH SULPHANILAMIDE.

No. and Age.	Blood culture BHS.[4]	Day of disease treatment started.	Dosage.[1]					Therapeutic effect.		Complications.			Area involved and degree.	Remarks.[3]
			Gm.	Per day Interval.	Days.	Total.		Spread of lesion.[2]	Day of disease recovery occurred.	Infectious.	Due to drug.			
						Gm.	Days.				Cyanosis.	Drug fever.		
1 33	–	3	0.25^5 0.125^5	q. 4 h. q. 4 h.	6 1	9.75^5	7	+	9	–	–	–	Face Sev.	Treatment inadequate. Course unaffected.
2 50	–	7	0.25^5 0.125^5	q. 4 h. q. 4 h.	2 2	4.25^5	4	±	11	–	–	–	Face Mild	Treatment inadequate.
3 79	–	1	0.6	t. i. d.	3	5.4	3	+	3	–	–	–	Face Mod.	Treatment inadequate.
4 70	–	3	1.2 0.6	q. i. d. q. i. d.	2 5	20.7	7	–	5	–	+	+	Face Mod.	Acute mastoid; cleared promptly without operation. Drug fever with rash, 9th day.
5 54	–	4	1.2 0.6	q. i. d. q. i. d.	3 4	24.0	7	±	8	–	–	–	Face Sev.	Lesion faded by 6th; fever persisted until 8th day
6 42	–	3	1.2 0.6	q. i. d. q. i. d.	2 3	15.6	5	–	5	–	–	–	Ear Mild	
7 40	–	4	1.5 0.6	q. 6 h. q. 6 h.	3 2	19.8	5	±	6	Abscess	–	–	Face Sev.	Abcess 10th day, 2 days after sulph. was stopped. Incision and drainage. Culture pos. BHS.
8 39	–	3	1.5 0.9	q. 6 h. q. 6 h.	4 2	28.2	6	–	5	–	–	–	Face Sev.	
9 42	–	3	1.5 0.6	q. 6 h. q. 6 h.	2 1	13.2	3	–	5	–	–	–	Face Mild	Otitis media. Patient left hospital before otitis subsided.
10 65	–	2	1.2 0.25^5	q. 6 h. q. 6 h.	3	14.7 2.75^5	3	±	D	–	+	–	Face Sev.	Acute nephritis, uremia, died 5th day. Dosage too high in view of nephritis. No autopsy.
11 1	–	3	0.3	q. 6 h.	7	7.3	7	–	5	–	–	–	Face Mod.	
12 42	–	4	1.2 0.6	q. 6 h. q. 6 h.	3 4	21.6	7	+	6	–	–	–	Face Sev.	Spread in spite of adequate dosage.
13 12	–	3	1.2 0.6	q. 6 h. q. 6 h.	4 5	22.4	9	–	4	–	+	–	Face Mod.	Cervical adenitis; subsided without surgery.

14 5 da.	+[6]	1	0.6[7] 0.2[7]	q. d. q. d.	4 3	3.0[7]	7	±	2	Abscess	−	−	Abd. Sev.	Abscess of scrotum 15th day, 3 days after discharge. Incision and drainage. Culture positive BHS. Recovered.
15 73	−	4	1.2 0.6	q. 6 h. q. 6 h.	2 4	18.0	6	±	5[8]	−	−	−	Face Mod.	Pul. tb.?, acute neph. Died 19th day, 10 days after sulph. was stopped. Autopsy: pul. tub., acute neph., congestion with slight necrosis of liver.
16 70	−	5	1.2 0.6	q. 6 h. q. 6 h.	3 4	22.8	7	−	6	Recurrence	+	−	Neck Sev.	Ca. of larynx, tracheotomy. Recurrent erysip. 21st day, 10 days after sulph. was stopped.
17 32	−	6	1.5 0.6	q. 6 h. q. 6 h.	3 4	27.3	7	±	8	−	+	−	Face Sev.	
18 54	−	4	1.5 0.9	q. 6 h. q. 6 h.	3 4	32.9	7	−	7	−	+	+	Leg Sev.	?Chr. cholecystitis. Drug fever with hepatitis 10th day. Recovered when drug was stopped.
19 15	−	3	0.9 0.6	q. 6 h. q. 6 h.	4 2	18.3	6	±	4	−	−	−	Leg Mod.	
20 50	−	1	1.5 0.9 0.6	q. 6 h. q. 6 h. q. 6 h.	3 2 3	26.7	8	±	3	−	+	−	Face Sev.	Otitis media, pernicious anemia.
21 61	−	3	1.5 0.9 0.6	q. 6 h. q. 6 h. q. 6 h.	2 2 3	26.3	7	−	4[8]	−	+	+	Face Sev.	Drug fever without rash 9th day. Cerebral hem. 17th day; expired 2 days later. No autopsy.
22 53	−	2	1.2 0.6	q. 6 h. q. 6 h.	6 2	28.2	8	±	6	−	+	+	Face Mod.	Otitis media. Drug fever with rash 10th day, 1 day after sulph. was stopped.
23 65	−	3	1.2 0.6	q. 6 h. q. 6 h.	4 2	19.2	6	−	5	−	+	+	Leg Mod.	Nephrosclerosis. N. retention 8th day. Drug fever with rash 10th day, 2 days after sulph. was stopped.
24 19	−	2	1.2 0.9	q. 6 h. q. 6 h.	2 2	12.6	4	−	3	−	−	−	Leg Mod.	
25 9 da.	+[6]	1	0.6[7] 0.3 0.3	q. d. b. i. d. q. d.	4 6 3	7.6	13	±	3	−	+	−	Pub. Sev.	Dramatic recovery.
26 50	−	2	1.2 0.9	q. 6 h. q. 6 h.	3 4	23.7	7	±	5	−	−	−	Face Sev.	Diabetes mellitus. Transient arthritis and albuminuria 15th day, 7 days after sulph. was stopped.
27 42	−	3	1.2 0.6	q. 6 h. q. 6 h.	4 4	23.7	8	±	6	−	+	−	Face Sev.	Intermittent low fever through 10th day when sulph. was stopped.

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[1] These data apply to this table and subsequent ones as well: Unless otherwise stated "Dosage" refers to oral administration of sulphanilamide tablets 0.3 gm. (5 gr.) "Prontylin"—Winthrop. Crystalline sulphanilamide (Merck) was used subcutaneously and intrathecally in 0.8% solution in physiological saline. "Prontosil" (Winthrop) Disodium salt of 4-sulphamido-phenyl-2 azo-7-acetylamino-1-hydroxynaphthalene-3, 6 disulphonic acid was always given intramuscularly. Discrepancies between "per day" and "total" columns depend on the hour the medication was started, changed or discontinued.

[2] − = No noticeable spread of lesion; ± = slight marginal spread during first 12 hours of treatment; + = definite spread after the first 12 hours of drug therapy.

[3] "Day" means day of disease unless otherwise specified, in this and following tables.

[4] BHS = Beta-hemolytic streptococcus [5] "Prontosil." [6] + = BHS 1 org./cc. [7] Subcutaneous. [8] Day of recovery from erysipelas.

TABLE 2.—CASES OF BETA-HEMOLYTIC STREPTOCOCCIC PNEUMONIA TREATED WITH SULPHANILAMIDE.

No. and Age.	Bacteriology—BHS.			Day of disease treatment started.	Dosage.					Therapeutic effect.		Complications.			Remarks.
	Blood culture.	Sputum culture.	Pleural fluid culture.		Gm.	Per day Interval.	Days.	Total. Gm.	Total. Days.	Spread of infiltration.	Day of disease recovery occurred.	Infectious.	Due to drug. Cyanosis.	Due to drug. Drug fever.	
1 58	+[1]	+[2]	+	4	0.375[3] 0.6 1.2 0.6	q. 6 h. q. 6 h. q. 6 h. q. 6 h.	4 3 3 8	5.6[3] 34.2	4 14	–	8	–	–	–	RML, RLL, empyema. Pleural fluid absorbed rapidly after 7th day. Surgical treatment unnecessary. Recovered.
2 30	+[4]	+[5]	...	4	1.5 0.6	q. 6 h. q. 6 h.	3 1	16.8	4	–	6	–	–	–	RLL. Pneumothorax 2d and 3d days for relief of pleural pain.
3 3	–	+[6]	...	9	0.6	q. 6 h.	5	4.5	5	–	12	–	–	–	LLL. Patient refused some of medication.
4 20	–	+	...	2	1.5 0.9 0.6	q. 6 h. q. 6 h. q. 6 h.	3 3 3	31.8	9	–	4	–	+	–	RLL.
5 3	–	–	...	3	0.6 0.6 0.3	q. 6 h. q. 8 h. q. 8 h.	4 5 4	21.3	13	–	7	–	+	–	LLL, postscarlatinal.
6 14	–	+	+	4	0.125[3] 1.2 0.9 0.6	q. 6 h. q. 6 h. q. 6 h. q. 6 h.	6 22 7 25	2.5[3] 201.6	6 54	–	27	–	+	–	LLL, empyema. Pleural fluid sterile after 17th day. Thoracotomy on 36th day, as fluid failed to absorb. Still under treatment for chr. empyema.
7 37	+[7]	+	...	8	1.5 1.2 0.6	q. 6 h. q. 6 h. q. 6 h.	12 9 2	115.5	23	–	49	–	+	–	RUL, cystic disease of lung. Lung clear by 26th day. Irregular fever through 49th day. Secondary anemia; subsided when sulph. was stopped. Recovered.

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[1] BHS 1 org./cc.

[2] BHS and Pneumococcus XXI.

[3] "Prontosil."

[4] BHS and Pneumococcus IV < 1 org./cc.

[5] BHS and Pneumococcus IV

[6] Lung puncture.

[7] BHS < 1 org./cc.

Bliss and Long,[1] Marshall *et al.*[13] and others has contributed significantly to the experimental approach to the problem. Reports of Colebrook and Kenny,[3] Long and Bliss,[12] Schwentker *et al.*[16] and others have added to the rapidly accumulating mass of clinical experience with the chemotherapy of beta-hemolytic streptococcic infections. Complications encountered in the use of sulphanilamide and its derivatives have been reported by Frost,[9] Foulis and Barr,[8] Southworth,[17] Discombe,[6] Plumer,[15] and Paton and Eaton,[14] and they have been mentioned incidentally by others.

In the present report a series of 114 consecutive cases of beta-hemolytic streptococcic infection, treated with sulphanilamide at this hospital, is presented.

Method. At the start of this study it was decided to treat all cases of proven beta-hemolytic streptococcic infection, as the material available was thought insufficient to evaluate the effect of the drug if alternate cases were treated. In addition, it was felt that by treating all cases a better estimate of human tolerance for sulphanilamide and its derivatives would be obtained. Studies of blood or urine sulphanilamide concentrations were not carried out in this series.

Dosage. In general, the plan followed was that outlined by Long and Bliss,[12] *i. e.*, (1) oral sulphanilamide: 1 gm. per day per 20 pounds of body weight up to 100 pounds, divided into 4 doses given at 6-hour intervals but not more than a total of 5 or 6 gm. per day in persons weighing over 100 pounds; (2) parenteral sulphanilamide: 0.8 gm. per 40 pounds of body weight per day (given in 0.8% solution in physiologic saline); (3) "Prontosil"—1 cc. per pound per day given intramuscularly in divided doses at 6-hour intervals. A few cases treated early in this study received doses considerably below what is now considered to be adequate. Likewise, several cases were given doses which are somewhat larger than that which is now considered maximal. It is felt that 5 gm. per day represents the maximum therapeutic dose of sulphanilamide given orally, 3.2 gm. the maximum dose to be given parenterally per day. To be sure, these figures are tentative and are subject to change, depending on future experience as well as variability in absorption, tolerance and further blood sulphanilamide concentration studies.

Prontosil was used to some extent early in this study. However, crystalline sulphanilamide for parenteral use was later used because it seemed more effective and convenient as well as less expensive.

Oral sulphanilamide seemed to be the preferable method of administration and it is felt that parenteral administration is only indicated where oral medication is impracticable.

Results. *Erysipelas.* The results in 27 cases of erysipelas are, on the whole, quite satisfactory (Table 1). Twenty-seven cases of erysipelas treated in this hospital between January 1, 1936, and January 1, 1937, were reviewed and the results were compared with those obtained in cases treated with sulphanilamide. Though such a comparison serves as a poor substitute for a series of alternately treated cases, certain interesting facts were revealed. The duration of the disease was 13.9 days in the control group as compared to 5.3 in the group treated with sulphanilamide. Spread of the local lesion was noted in 66% (18 cases) of the control series, while only 11% (3 cases, 1, 3 and 12) of the treated series showed more than

TABLE 3.—CASES OF BETA-HEMOLYTIC STREPTOCOCCIC MENINGITIS TREATED WITH SULPHANILAMIDE.

No. and Age.	Diagnosis.	Bacteriology—BHS.	Day meningitis treatment was started.	Dosage.					Therapeutic effect.		Complications.			Remarks.
							Total.					Due to drug.		
				Gm.	Per day Interval.	Days.	Gm.	Days.	Spinal fluid.	Day meningitis fever disappeared.	Infectious.	Cyanosis.	Drug fever.	
1 19	Meningitis, septicemia	Bl. cult. < 1 org./ cc.; sp. fluid: smear +, cult. +, cell count 34,250, 98% polys.	2	0.75[1]	q. 6 h.	1	0.75[1]	1	None	–	–	–	–	Strep. meningitis developed during convalescence from meningococcic meningitis. Death 5 hours after treatment was started.
2 25	Meningitis, septicemia. Cavernous sinus thrombosis. Pansinusitis	Bl. cult. BHS and H. influenza < 1 org./cc.; sp. fluid: Smear –. Cult. BHS and H. influenza. cell count 1150, 98% polys.	4	0.625[1]	q. 6 h.	3	6.25[1]	3	None	–	–	–	–	Death 6th day, 3d day of treatment.
3 13	Meningitis. Mastoiditis, acute	Bl. cult. sterile; sp. fluid: smear +, culture +, cell count 2460, 97% polys.	4	0.9 1.2	q. 6 h. q. 6 h.	5 3	28.2	8	Excellent[2]	16[3]	–	+	+	Mastoidectomy 2d day; spinal fluid negative at this time; 4th day temp. rose, sulph. started. Drug fever without rash 4th day of treatment. Recovered.
4 7	Meningitis. ?Cavernous sinus thrombosis. Hemiparesis.	Bl. cult. < 1 org./cc.; sp. fluid: smear +, cult. +, cell count 44,250, 98% polys.	4	0.15[4] 1.6[5] 0.9 0.6	q. d. q. d. q. 6 h. q. 6 h.	4 3 5 6	30.8	14	Excellent[6]	15	+	+	–	Sterile int. hydrocephalus with incr. pressure on 18th day requiring surgery. Still under treatment.
5 52	Meningitis, septicemia. Orbital cellulitis. Cavernous sinus thrombosis	Bl. cult. 30 org./cc., sp. fluid: smear +, cult. +, cell count 640, 100% polys.	3	0.2[4] 3.0[5]	q. d. q. d.	2 2	6.4	2	None	–	–	+	–	Dead 5th day. Moribund when treatment was started.

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[1] "Prontosil."

[2] Spinal fluid sterile on 9th day of meningitis and thereafter (not examined between 5th and 9th days of meningitis because meningeal signs had decreased markedly).

[3] Fever of disease merged with drug fever.

[4] Intrathecally.

[5] Subcutaneously.

[6] Sterile on 6th day of meningitis and thereafter.

slight marginal spread. Of these only 1 (Case 12) is now considered to have been adequately treated and even in that instance recovery occurred promptly. Two cases (14 and 25) are outstanding in view of the high mortality of erysipelas in infants in the presence of a positive blood culture (94%).[5] Infectious complications occurred in 3 cases. Abscesses formed in 2 cases (7 and 14) 3 and 8 days respectively after sulphanilamide had been discontinued. Recurrent erysipelas developed in Case 16 10 days after withdrawal of the drug. Of the 3 fatal cases (10, 15 and 21), the cause of death in 2 (15 and 21) did not seem attributable to the erysipelas or the treatment. In the third case (10) the erysipelas had faded completely and the patient died of kidney insufficiency, possibly aggravated by sulphanilamide.

Pneumonia. In a group of 7 cases (Table 2), there were 3 (1, 6 and 7) which had purulent complications at the time treatment was begun. In these cases the course was noticeably more protracted, with one exception (Case 1). Two of the cases (1 and 7) subsided without surgery, while 1 (Case 6) required a thoracotomy, even though the pleural exudate had become sterile. In this case and 2 others subsequently treated, the course of streptococcal empyema seems to have been transformed into a subacute inflammation in which considerable organization, thickening of pleura and contraction of the chest created therapeutic problems of considerable significance. The remaining cases had no purulent complications at the onset and developed none after sulphanilamide was started. Recovery in these cases was more prompt. All cases recovered.

Meningitis. Among 5 cases of meningitis (Table 3), 2 recovered (Cases 3 and 4): However, 1 of these (Case 4) developed an internal hydrocephalus in spite of the fact that the infection had subsided. Of the 3 cases which expired, only 1 might possibly be regarded as a therapeutic failure (Case 5). The other 2 fatal cases (1 and 2) could hardly be called failures, as the former died 5 hours after treatment was started and the latter had a mixed infection. The 2 recoveries represent the only cases which have survived a beta-hemolytic streptococcic meningitis in this hospital in the past 10 years.

Mastoiditis. In a group of 15 cases of mastoiditis (Table 4) only 2 patients (7 and 13) required mastoidectomy after sulphanilamide was started. In other words, 9 cases subsided without surgical treatment. Case 15, which showed marked meningeal reaction, is perhaps the most striking one to recover without surgical intervention. None of the cases developed any infectious complications after sulphanilamide was started. All cases recovered.

Otitis Media. Eleven cases of otitis media (Table 5) subsided, 2 (Cases 2 and 7) without developing discharge. In 1 instance (Case 11) relapse occurred, but discharge promptly subsided when sulphanilamide was given. Mastoiditis or other infectious compli-

TABLE 1.—CASES OF BETA-HEMOLYTIC STREPTOCOCCIC MASTOIDITIS TREATED WITH SULPHANILAMIDE.

No. and Age.	Bacteriology—BHS.			Day mastoiditis treatment was started.	Dosage.					Myringotomy.	Mastoidectomy.	Therapeutic effect.		Complications.			Remarks.
								Total.							Due to drug.		
	Blood culture.	Ear culture.	Mastoid culture.		Gm.	Per day Interval.	Days.	Gm.	Days.			Day of disease aural disch. ceased.	Day of disease fever disappeared.	Infectious.	Cyanosis.	Drug fever.	
1 20	....	+	...	3	1.2	q. 6 h.	5	22.8	5	...	...	7	4	–	–	–	Pharyngitis subsided.
2 3	....	+[1]	...	20	0.6	q. 8 h.	6	10.8	6	+[2]	...	23	Afebrile	–	–	–	Bilat., with Roentgen ray evidence of destruction. Both subsided.
3 11	–	+	+	9	0.9 0.6	q. 6 h. q. 6 h.	4 10	37.2	14	+[2]	+[2]	26	15	–	+	–	Subperiosteal abscess.
4 10	–	+	..	6	0.9 0.6	q. 6 h. q. 6 h.	6 16	59.4	22	+[2]	...	23	10	–	–	–	Pharyngitis subsided.
5 8	–	+	....	7	0.9 0.6	q. 6 h. q. 6 h.	6 3	27	9	+[2]	...	21	9	–	+	+	Sinusitis and tonsillitis subsided. Drug fever with rash on 16th day of sulph.
6 4	....	+	+	7	0.6	q. 6 h.	15	32.9	15	+[2]	+[2]	15	12	–	–	–	Subperiosteal abscess.
7 9	+[3]	+	+	6	0.6	q. 6 h.	30	71.1	30	+[2]	+	25	16	–	+	–	Jug. vein thrombosis. Mastoidectomy, 9th day. Improved after operation.
8 5	–	+	....	3	0.6 0.3	b. i. d. b. i. d.	20	36.0	20	+[2]	...	13	7	–	–	–	Sinusitis subsided.
9 9	–	+	+	13	0.9	q. 6 h.	8	27.5	8	+[2]	+[2]	21	18	–	+	–	
10 10	....	+	....	13	0.9 0.6	q. 6 h. q. 6 h.	3 3	16.5	6	+[2]	...	20	Afebrile	–	–	–	
11 12	–	+	....	2	0.9 0.6	q. 6 h. q. 6 h.	2 10	31.1	12	+[2]	...	12	Afebrile	–	+	–	
12 9	–	+	....	7	0.6	q. 6 h.	10	23.9	10	+[2]	...	15	8	–	–	–	Sinusitis subsided.
13 18	–	+	+	3	1.2 0.6	q. 6 h. q. 6 h.	10 7	59.4	17	+[2]	+	19	8	–	+	–	Mastoidectomy on 7th day, with marked improvement.
14 15	....	+	+	16	1.2	q. 6 h.	11	51.6	11	...	+[2]	30	23	–	–	–	
15 5	–	+	....	3	0.25[4] 0.9 0.6	q. 6 h. q. 6 h. q. 6 h.	2 4 5	1.5[4] 25.2	2 9	+[2]	...	8	8	–	+	–	Mening. irrit., Roentgen ray evidence of destructive mastoiditis; 4000 cells in sp. fluid; cult. repeatedly neg.

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[1] Bilateral.

[2] Done at the time sulphanilamide was started or before.

[3] BHS < org./cc.

[4] "Prontosil."

TABLE 5.—CASES OF BETA-HEMOLYTIC STREPTOCOCCIC OTITIS MEDIA TREATED WITH SULPHANILAMIDE.

No. and Age.	Bacteriology—BHS.		Day of otitis when treatment was started.	Dosage.					Myringotomy.	Therapeutic effect.		Complications.			Remarks.
	Blood culture.	Ear culture.		Gm.	Per day Interval.	Days.	Total.			Day of disease when disch. ceased.	Day of disease when fever disappeared.	Infectious.	Due to drug.		
							Gm.	Days.					Cyanosis.	Drug fever.	
1 1.5	—	+	2	0.3 0.3	q. 6 h. b. i. d.	6 5	9.6	11	. . .	13	2	—	—	—	Cerv. aden. and tonsillitis subsided.
2 6	—	—[1]	2	0.6 0.3	q. 6 h. q. 6 h.	4 7	17.4	11	. . .	None	3	—	—	—	Cerv. aden. and pharyngitis subsided.
3 9	. . .	+	20	0.6	q. 6 h.	11	24.6	11	+[2]	28	31	—	—	—	
4 10	. . .	+	8	0.6	q. 6 h.	6	14.2	6	. . .	13	13	—	+	—	
5 0.5	—	+	5	0.3	q. 6 h.	26	30.0	26	+[2]	22	5	—	—	—	Course unaffected.
6 50	. . .	+	16	1.2 0.6	q. 6 h. q. 6 h.	10 5	58.2	15	+[2]	34	25	—	+	—	Sinusitis subsided.
7 3	—	. . .[3]	3	0.6 0.3	q. 6 h. q. 6 h.	4 2	9.3	6	. . .	None	5	—	—	—	Tonsillitis subsided.
8 10	. . .	+	5	0.9 0.6	q. 6 h. q. 6 h.	4 6	21.9	10	. . .	11	5	—	+	+	Drug fever with rash on 14th day, 10th day of sulph.
9 0.7	—	+	14	0.3	q. 6 h.	10	10.8	10	. . .	24	15	—	—	—	
10 41	. . .	+	4	1.2	q. 6 h.	3	9.6	3	+[2]	?	5	—	+	—	Left hospital before otitis cleared completely.
11 1.5	—	+	15	0.3	q. 6 h.	12	13.2	12	+[2]	28	Afebrile	Relapse	—	—	Relapse 4 days after sulph. was stopped. Treatm. reinstituted, discharge ceased in 2 days, 33d day. Cerv. aden. subsided without surgery.

[1] BHS in nose and throat cultures.

[2] Myringotomy done at the time sulphanilamide was started or before.

[3] BHS in throat culture.

Table 6.—Miscellaneous Cases of Beta-hemolytic Streptococcic Infection Treated With Sulphanilamide.

No. and Age.	Diagnosis.	Bacteriology—BHS.		Day of disease treatment was started.	Dosage.					Surgical treatment.	Therapeutic effect.		Complications.			Remarks.
		Blood culture.	Other cultures.		Gm.	Per day Interval.	Days.	Total.			General.	Day of disease when fever disappeared.	Infectious.	Due to drug.		
								Gm.	Days.					Cyanosis.	Drug fever.	
1 60	Cellulitis of leg; presumably streptococcal	—	+ (throat)	7	1.5 0.6	q. 6 h. q. 6 h.	5 8	45.0	13	. . .	None	17	Abscess	—	—	Abscess 13th day, drained. Cult. of abscess sterile.
2 22	Cellulitis of chest wall; thoracotomy	—	+ (throat and lesion)	2	1.5 0.9 0.6	q. 6 h. q. 6 h. q. 6 h.	4 4 2	40.8	10	. . .	Excellent	5	Abscess	+	—	Abscess 20th day, 8 days after sulph was stopped. Incision and drainage. BHS cultured from abscess.
3 40	Tenosynovitis, little finger; palmar abscess	—	+ (wound)	13	0.6 (inadequate dosage)	t. i. d.	8	13.8	8	I. & D.[1]	None	16	Relapse	+	—	Relapse 30th day, 18 days after sulph. was stopped. I. & D. repeated and sulph. given in larger doses, but course unaffected. Recovery slow.
4 7	Tenosynovitis, index finger	. . .	+ (wound)	4	0.6	q. 6 h.	10	21.6	10	I. & D.[1]	Excellent	Afebrile	—	—	—	
5 44	Septicemia; fracture 1st lumbar vertebra	+[2]	+ (throat)	2	1.5	q. 6 h.	6	33.9	6	. . .	Satisfactory[3]	7	Relapse	+	—	NPN 110 7th day, sulph stopped. Bl. cult. again pos., 15th day. Sulph. again given; bl. cult. sterile 18th day and thereafter. No N. retention in second course of sulph. Recovered.
6 76	Septicemia; hemorrhagic pneumonia; erysipelas; art. heart dis.	+[4]	+ (throat)	2	1.2	q. 6 h.	1	1.2	1	. . .	None	. . . .	—	—	—	Death 4 hrs. after sulph. was started.
7 49	Abscess of scalp; post-craniot.	—	+ (wound)	3	1.5 1.2 0.9 1.5 1.2 0.6 0.9	q. 6 h. q. 6 h. q. 6 h. q. 6 h. q. 6 h. q. 6 h. q. 6 h.	3 4 5 7 17 21 21	290.0	78	Drainage	None	Still febrile	Relapse	+	+	Drug fever without rash on 13th day. Infection persists; cult. remain pos. for BHS after 78 days of treatment.

[1] Incision and drainage done before or at start of sulph. therapy.
[2] BHS 100 organisms per cc.
[3] Blood culture sterile on 7th day of disease.
[4] BHS 30 organisms per cc.

cations did not develop in any instance after treatment was started. All cases recovered.

Miscellaneous (Table 6). Two cases of cellulitis (Cases 1 and 2) were treated. The former showed no response to sulphanilamide. The etiology of this case, however, was never proven. The fact that the culture of the abscess was sterile might possibly be of significance. Case 2 showed a good response initially, but an abscess containing beta-hemolytic streptococci developed after treatment was discontinued. One case of tenosynovitis (Case 3) showed no response but the dosage might have been inadequate. The course of another case (4), on the other hand, was quite satisfactory. Case 5, one of septicemia, responded fairly well but developed nitrogen retention and the drug had to be discontinued. When the septicemia recurred, response was again satisfactory and the drug was well tolerated at a somewhat smaller dosage. The lack of response in Case 6 could hardly be attributed to the failure of sulphanilamide as the patient was moribund when treatment was instituted. Case 7 is an example of therapeutic failure, as beta-hemolytic streptococci persisted in this patient's draining scalp wound after 2½ months of treatment. However, during the first 3 weeks of therapy in this case, spinal fluid drained profusely through the infected wound and the fact that meningitis or intracranial infection did not develop might be of significance.

Other Cases. Seven cases of scarlet fever were treated, 4 of which received no serum. The toxic phase of the disease seemed unaffected by sulphanilamide. There were, however, no septic complications in the group. In a series of 9 cases of purulent sinusitis, only 1 required surgical treatment after sulphanilamide was started, and that patient had a mixed infection. At operation, only pneumococci were found in the sinus culture. Among 11 treated cases of lymphadenitis, only 2 required surgical therapy after treatment was started and 1 of these had a mixed infection. Adenitis recurred in 2 cases, but in each case responded satisfactorily to sulphanilamide. Sixteen cases of pharyngitis and tonsillitis responded fairly promptly and none developed infectious complications.

Infectious Complications. Infectious complications were encountered in 10 of the 114 cases (8.7%). In retrospect, one might attribute these in some cases to inadequate dosage or too rapid withdrawal of the drug. Such an incidence detracts materially from the good results obtained. Perhaps the number of such complications may be reduced appreciably when more exact methods are employed in determining dosage and duration of treatment.

Complications Attributed to Sulphanilamide. In the present group of cases complications were frequent, various, prominent and sometimes severe (Table 7). Cyanosis was by far the most frequent, in fact one might question whether it is really a complication or a natural concomitant of the administration of this drug. Spectroscopic studies of the venous blood of 5 cases (courtesy of Dr. Kurt

TABLE 7.—COMPLICATIONS DUE TO SULPHANILAMIDE ENCOUNTERED IN THE TREATMENT OF 114 CASES OF BETA-HEMOLYTIC STREPTOCOCCIC INFECTION.

	Cases.	Percentages.
Cyanosis	51	44.7
Drug Fever	17	14.9
With rash	9	7.9
Without rash	8	7.0
Nitrogen retention	3	2.6
Hepatitis	1	0.9
Secondary anemia	1	0.9
Thrombocytopenia	1	0.9
Granulopenia	0	0.0
Total number of cases showing complications excluding cyanosis	22	19.3
Total number of cases showing complications	56	49.1

Stern) revealed evidence of methemoglobinemia, estimated to represent 5 to 15% of the total hemoglobin. In general, it was felt that the degree of cyanosis was too great to be entirely explained on the basis of the degree of methemoglobinemia present. In one instance, by oxygen capacity studies, 16% of the hemoglobin was found to be present as methemoglobin. Only 2 patients of the 114 treated had any exposure to magnesium sulphate or other saline cathartics, that being in the form of soaks in both instances. Cyanosis was present in both cases, but was in no way remarkable in type or degree. In one of these cases spectroscopic examination of the blood revealed evidence of methemoglobin and no sulphhemoglobin.

In 14.96% of the cases a febrile reaction was noted, occurring with or without a rash and coming on usually between the seventh to tenth day of the drug therapy. To distinguish this type of reaction, the term Drug Fever is suggested. This phenomenon has many features which suggest a similarity to Serum Disease. More complete data and details on this type of reaction have been published.[11]

Nitrogen retention developed during therapy in 3 instances; subsided promptly in 2 of these when the drug was discontinued. One of the cases which recovered had no known preëxisting kidney disease. The third case had acute nephritis when treatment was started and later developed uremia and died.

In one instance toxic hepatitis was noted in a patient with probable chronic cholecystitis. Recovery occurred when the drug was discontinued. Secondary anemia out of proportion to that expected from the disease developed in 1 case and this condition promptly corrected itself when the drug was discontinued. One patient was sent to this hospital with thrombocytopenic purpura. He had been taking sulphanilamide, salol and phenacetin in small dosages while being treated for pharyngitis and cervical adenitis. This patient gradually recovered and, although the etiology is not proven, it seems quite likely that sulphanilamide might have played a part in the etiology of the blood dyscrasia. No cases of neutropenia were noted in the present series.

Comment and Conclusions. Because of the fact that the course of the infectious diseases reported on is extremely variable, it has been difficult to evaluate the results observed in this group of cases. The impression has been gained, however, that sulphanilamide favorably modifies the course of beta-hemolytic streptococcic infections in the majority of instances, although the results presented fall far short of proving this point. Such proof can only be forthcoming through compilations of similar series and more extensive and accurately controlled studies.

In addition, it is apparent that sulphanilamide is far from being non-toxic. When a therapeutic agent causes an illness which may occasionally be more severe than the initial infection, one is forced to consider seriously before advocating its widespread usage, at least for the milder forms of streptococcic infection. Certainly the indiscriminate use of the drug in the absence of bacteriologic or clinical indications is to be condemned. The toxic phenomena described are all relatively immediate in making their appearance. To what extent delayed toxic reactions will occur and what their nature and severity may be, of course, remains to be learned.

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EXPERIENCE WITH SULPHANILAMIDE IN MENINGITIS.

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During the past few months we have been much interested in the possibilities of the use of sulphanilamide in the treatment of meningitis. The object of this paper is not to review the extensive literature which has already been published in regard to this chemical and the results of its use but rather to record briefly our own experience with it.

It must be admitted that the potentialities of sulphanilamide are not as yet completely known. It may be said without much danger of contradiction that it is of great value in the treatment of infections with the hemolytic streptococcus. We believe that our observations have proved this to be so in the case of meningitis due to this organism.

There is good evidence, both from experimental and clinical studies, to indicate that it is of value in infections with the meningococcus. Our own experience in this connection has been encouraging, but up to the present time has been limited. The results of Schwentker, *et al.*[3] have been decidedly encouraging.

Experimental studies indicate that this chemical is of value in pneumococcic infections. The clinical results have been indefinite. Our own experience, however, indicates that sulphanilamide may be effective at times in pneumococcic meningitis.

Preliminary experiments performed by Dr. Olga Provitzky indicate that a combination of Prontosil and immune serum has some curative action on otherwise fatal inoculations in mice with influenza bacilli (isolated from spinal fluids).

The mode of action of this chemical is not known. It has however, been shown by Marshall, Emerson and Cutting that it has the remarkable power of penetrating all tissues, including bone and fat. This particular quality may be an important factor in its effectiveness. Marshall further points out that the chemical is readily absorbed into the general circulation and that its concentration in the spinal fluid is nearly equal to that in the blood even after oral administration.

Sulphanilamide and its various derivatives have been used too short a time to admit of definite conclusions in regard to the optimum dosage and the best methods of administration. The preparations that we have used are Prontosil intramuscularly, Prontylin orally and at times an 0.8% solution of Prontylin crystals intraspinally. It is our impression that it is not necessary to use the large doses advocated by certain workers. As a rule, we have given 5 cc. or less of the Prontosil every 4 hours to younger children and 10 cc. every 4 hours to older children and adults. In addition, from 5 to 15 grains of Prontylin have been given every 6 hours. We have felt that the use of the combination was preferable to either agent alone. With evidence of definite clinical improvement the Prontosil was usually discontinued but the Prontylin was continued for a variable period.

While there are references to the use of a solution of Prontylin crystals subcutaneously, we have administered it only intraspinally. An 0.8% solution is prepared by dissolving the crystals in hot normal saline. The fluid is then allowed to cool to body temperature and is administered intraspinally by gravity, in a dose of 10 to 25 cc. The unused part of the solution may be kept under sterile precautions for several days. If the crystals precipitate out, as they will if the solution is kept in a cold place, they will redissolve by warming to 45° to 50° C.

We do not feel sure at present that there is any advantage in administering the sulphanilamide intraspinally. Indeed most of our recovered cases were not treated in this manner. We have already referred to the observation of Marshall, *et al.*[2] regarding the high concentration of sulphanilamide in the spinal fluid following oral administration. However, the 0.8% sulphanilamide solution is non-irritating to the meninges and can do no harm. There may also be an advantage from a mechanical point of view in replacing a certain amount of the spinal fluid withdrawn. Prontosil should not be used either intravenously or intraspinally.

There has been considerable discussion in regard to the toxic effects of sulphanilamide. We have not observed such effects in any alarming degree. We realize of course that an occasional patient may be unduly sensitive to this as to any other chemical. If the patient already has marked anemia or cyanosis or impairment of renal function the drug should be used with caution. It is no doubt advisable to make repeated blood counts during the period of treatment.

We have used sulphanilamide in cases of meningitis due to the hemolytic streptococcus, the pneumococcus, the meningococcus and the influenza bacillus. We have also used it in a group of miscellaneous cases including meningococcemia.

The use of sulphanilamide in cases of hemolytic streptococcic meningitis have yielded results that seem to us quite astounding. While the number of cases is still small the results have been almost uniformly favorable. We have had 17 cases. All but one of these have been secondary to infections of the ears or mastoids. The exception was a case associated with a pansinusitis.

The diagnosis in these cases was definitely established by recovering the hemolytic streptococcus from the spinal fluid culture. In this connection it is important to stress that certain strains of this organism will hemolyze only horse blood and in media which do not contain sugar.

Another case of meningitis, in which scarlet fever was followed by double otitis media and right mastoidectomy, was probably due to a hemolytic streptococcus. The spinal fluid was purulent, showed marked diminution in sugar and Gram-positive cocci in smear on two occasions. However, the culture did not grow. This patient recovered. She received convalescent scarlet fever serum in addition to the sulphanilamide.

Of the 17 cases in which there was no question of the diagnosis 4 have died and 13 have recovered.

The following table shows the more important points in regard to this group of cases:

TABLE 1.—CASES OF MENINGITIS DUE TO THE HEMOLYTIC STREPTOCOCCUS.

Case.	Sex*.	Age (yrs.)	Primary source of infection.	Treatment.	Result.	Remarks.
1	♀	21	Right maxillary sinusitis. Right otitis with mastoiditis	Drainage antrum; mastoidectomy, spinal drainage, sulphanilamide, convalescent scarlet fever serum	Recovered	Only a small amount of serum was given
2	♀	7	Left otitis with mastoiditis	Mastoidectomy, spinal drainage, sulphanilamide	Recovered	
3	♂	5½	Left otitis	Antimeningococcic serum (4 doses) spinal drainage, sulphanilamide	Recovered	
4	♀	43	Right otitis	Spinal drainage, sulphanilamide	Recovered	
5	♀	3½	Left otitis	Spinal drainage, sulphanilamide	Recovered	
6	♀	11	Right otitis with mastoiditis	Spinal drainage, sulphanilamide	Recovered	Refused operation and mastoiditis persisted after recovery from meningitis
7	♀	2	Double otitis with right mastoiditis, following scarlet fever	Right mastoidectomy with ligation right jugular, spinal drainage, sulphanilamide, convalescent scarlet fever serum	Died	Meningitis appeared 7 days after operation. Necropsy showed herniation of cerebellum and thrombosis of left lateral and transverse sinuses and of left jugular
8	♂	5½	Left otitis with mastoiditis, following pneumonia	Mastoidectomy, antimeningococcic serum, spinal drainage, sulphanilamide	Recovered	
9	♂	8	Right otitis with mastoiditis	Mastoidectomy 1 mo. prior to meningitis, spinal drainage, sulphanilamide	Recovered	Mastoidectomy done about 1 mo. before onset of meningitis. Spinal fluid showed positive culture for 14 successive days
10	♀	4	Left otitis with mastoiditis and later right otitis	Left mastoidectomy, spinal drainage, sulphanilamide	Recovered	At operation, left mastoid found necrotic. although no clinical signs
11	♂	35	Pansinusitis	Antimeningococcic serum, spinal drainage, sulphanilamide	Died	Sulphanilamide was used for less than 24 hours. Necropsy showed pansinusitis and sarcoma of pituitary
12	♀	12	Left otitis with mastoiditis	Mastoidectomy, spinal drainage, sulphanilamide, 1 dose antimeningococcic serum	Recovered	At operation mastoid found necrotic although no clinical signs
13	♀	10 mos.	Double otitis with double mastoiditis	Mastoidectomy, spinal drainage, sulphanilamide	Died	There was also clinical evidence of brain abscess. At operation dural plate found nearly destroyed. Sulphanilamide used for less than 12 hours
14	♀	8	Left otitis with mastoiditis	Mastoidectomy, spinal drainage, convalescent scarlet serum, sulphanilamide	Recovered	At operation, mastoid found necrotic although no clinical signs
15	♀	6½	Right otitis with mastoiditis	Mastoidectomy, spinal drainage, sulphanilamide	Died	Necropsy showed meningitis but no localized suppuration
16	♂	4	Following measles first left otitis with mastoiditis and later right otitis with mastoiditis	First left mastoidectomy and later right mastoidectomy, spinal drainage, sulphanilamide	Recovered	Meningitis appeared 12 days after left mastoidectomy. At this time a right mastoidectomy done
17	♂	7	Double otitis with double mastoiditis following scarlet fever	First left mastoidectomy and 3 weeks later right mastoidectomy, spinal drainage, sulphanilamide	Recovered	Onset of meningitis was about 12 days after the second mastoidectomy

* In this column: ♂ denotes male, and ♀, female.

It may be worth while to discuss briefly the 4 fatal cases. One patient had a double otitis media and double mastoiditis. There was also clinical evidence of a brain abscess and the dural plate was found to be nearly destroyed when the operation was performed. The patient died within 12 hours after the first dose of Prontosil. The second case was one of severe pansinusitis of long standing and meningitis of several days' duration. He was in a grave condition and died within 24 hours after starting the sulphanilamide. The necropsy showed extensive suppuration of the meninges and sinuses including the sphenoidal and a large spindle-cell sarcoma of the pituitary body. The third patient had a right mastoidectomy following otitis media. There was quite marked improvement for a time but death finally ensued. At necropsy, no portal of entry was found in the gross and there was no evidence of any localized suppuration. The fourth patient had a double otitis media following scarlet fever, a right mastoidectomy, packing of the lateral sinus and ligation of the right jugular. The onset of the meningitis was 7 days later. She was adequately treated with sulphanilamide and also received scarlet fever convalescent serum both intraspinally and intravenously. She died 17 days after the onset of the meningitis. At necropsy, it was found that there was herniation of the cerebellum into the wound of the right mastoidectomy. There was also thrombosis of the left transverse and the lateral sinuses and left jugular vein. It may certainly be said that in the case of 3 of these patients, the first, second and fourth, the developments were such that the fatal terminations cannot be ascribed to a failure of action of the sulphanilamide.

A comparison of these results with those previously obtained by us is indeed striking. During the period of more than 26 years that the meningitis division has been in existence, the case fatality in hemolytic streptococcic meningitis has been uniformly very high. Up to the end of 1936 we had seen 274 cases of various kinds of streptococcic meningitis, most of which were the hemolytic variety. Of these only 15 recovered, of which 9 were definitely caused by the hemolytic streptococcus. There was a tenth recovery in which there was a mixed infection of the meningococcus and the hemolytic streptococcus. Three of these recoveries were in patients in whom the meningitis developed following scarlet fever. In two instances the antiscarlatinal serum was used and in the third, large amounts of convalescent serum and small amounts of Prontosil and Prontylin.

One may wonder if we are dealing at present with less virulent strains of the hemolytic streptococcus. Experiments in animals cannot prove this as there is no uniform relationship between the reaction in animals and the severity of the disease in the patient from whom the strain was isolated. It would seem remarkable if there has been a sudden change in virulence. During the year 1936 we saw 20 cases of hemolytic streptococcic meningitis all of which died with the exception of the third following scarlet fever to which we have already referred.

We have seen 14 cases of pneumococcic meningitis. The types of pneumococcus are shown in Table 2.

TABLE 2.

Type ..	I	III	IV	V	VI	VII	XIII	XXIX	XXXI	Beyond XXXI
Number	2	2	1	1	2	1	1	1	1	2

A fifteenth case showed a mixed infection of Pneumococcus III and Streptococcus viridans. The meningitis followed an operation on the ethmoid. The blood culture was positive for the pneumococcus. The patient died.

Of these 14 cases 3 recovered. The first was a Type XXXI meningitis which developed shortly after a tonsillectomy and an operation on the ethmoids. The second case (Type XXIX) followed within 48 hours after a submucous resection and an operation on a turbinate. The third patient (Type IV) had a double otitis media complicated by bilateral mastoiditis. A mastoidectomy was done first on right side and a week later on left side. Meningitis developed about a week after the second operation. The patient ran a fairly stormy course but recovered.

None of these patients who recovered received serum.

Of the 11 fatal cases only 2 had no history of a primary infection. In certain instances no definite focus could be located but there was a history of an upper respiratory infection immediately preceding the onset of the meningitis. Whenever a specific serum was available it was used in addition to the sulphanilamide.

While the clinical results with sulphanilamide in pneumococcic meningitis are not at all comparable to the results in meningitis due to the hemolytic streptococcus, they are nevertheless favorable when compared to our former case fatality which had been 100%. Furthermore, even in the fatal cases the illness was as a rule of a longer duration than in our previous experience.

Our experience with sulphanilamide in meningococcic infections has been too limited to warrant a detailed discussion. With one exception we have used this chemical as a supplement to the specific serum. The exception was a very severe case of meningitis due to the meningococcus and the hemolytic streptococcus. This patient suddenly developed respiratory failure, which, we believe, was due to a herniation of the cerebellum with compression of the medulla. However, no necropsy was obtained. In a few instances we have used Prontosil and Prontylin successfully in patients with a definite or probable meningococcemia who had become sensitive to serum. In 2 very severe cases of meningitis, one with a septicemia and joint involvement and the second in her fourth month of pregnancy, we believe that the sulphanilamide played a part in their rather rapid recoveries. In one instance the combined use of serum and sulphanilamide failed to check the progress of the disease. Toward the end the patient presented clinical evidence of brain abscess. Unfortunately, there was no necropsy.

It is our belief at the present time that the sulphanilamide should be used in conjunction with the specific serum, except in instances where the patients are sensitive to serum.

We have treated only one case of influenzal meningitis since we began the use of sulphanilamide. This patient received the anti-influenzal serum both intravenously and intraspinally and also Prontosil and Prontylin. She made a rapid recovery. Reference has already been made to experimental work by Dr. Povitzky in regard to the value of combined use of specific serum and Prontosil in infections by *B. influenzæ.*

We are certain that in the treatment of meningitis the use of sulphanilamide should be supplemented by such other methods of treatment as are indicated. In meningococcic meningitis the specific serum should certainly be used until further proof of the efficacy of sulphanilamide alone has been established. In streptococcic meningitis following scarlet fever it is probably advisable to use either the specific or the convalescent serum. In pneumococcic meningitis the value of serum is indefinite. When meningitis is due to *B. influenzæ* we believe that the anti-influenzal serum should be used.

It is important in all forms of meningitis adequately to drain the subarachnoid space. In our experience, the more radical methods of establishing drainage, such as laminectomy or trephining the cisterna magna, have no advantage over repeated lumbar punctures or cisternal or ventricular punctures if block occurs. Indeed, establishing permanent drainage may be a disadvantage if serum or chemicals are to be used intraspinally. Forced spinal or perivascular drainage has been used rather extensively during the past 4 or 5 years. We have had considerable experience with this method of treatment. As a result of our experience we do not recommend it.

Whenever the meningitis is secondary to a focus of infection it is important to eradicate this focus as completely and as promptly as possible. It cannot be too strongly emphasized that not infrequently a severe mastoiditis may fail to present clinical symptoms and occasionally even roentgenographic evidence of involvement (Table 1). Of course, a patient will occasionally recover even if the focus infection is not removed. But as a rule it is too great a risk not to eradicate the primary focus.

The general care of patients suffering from meningitis is always important. Proper attention should be paid to an adequate fluid intake and to elimination. It is of the utmost importance to keep the patient quiet even if it is necessary to use sedative.

Summary. We have discussed our experience in the use of sulphanilamide in the various forms of purulent meningitis. The results in meningitis due to the hemolytic streptococcus have been excellent and in pneumococcic meningitis encouraging. Our experience in meningococcic infections has been too limited for definite conclusions to be drawn. However, it is our impression that it is of value in these cases. We have also stressed the importance of additional methods of treatment.

Since this paper was written, an article has been published by Branham and Rosenthal[1] entitled "Sulphanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice." The following quotation is taken from this publication: "The combination of serum and drug therapy yielded much better results than either alone. In four experiments in which poor curative effects were obtained with serum or drug only, combined therapy resulted in the survival of most of the mice. A synergistic action seemed to exist, since the increased effectiveness of combined therapy was greater than the additive effects of drug and serum alone.

"The superiority of combined drug and serum therapy was likewise demonstrated in mice infected with Type I pneumococci.

"The results of these experiments suggest that a combination of drug and serum therapy in meningococcus and pneumococcus infection in man is worthy of trial."

We wish to thank the Winthrop Chemical Company for generously supplying us with Prontosil, Prontylin and Prontylin crystals.

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THE TOXICOLOGY OF CYANIDE.

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I. Analytical Methods. A. Quantitative Separation of Cyanide From Tissues. Isolation and complete recovery of cyanide (as HCN) from the tissues is essential before any quantitative method can be applied. Three procedures have been used for this purpose: ordinary distillation, steam distillation, and aëration. We have discarded the first two procedures in favor of the third because the volume of the distillate needed to recover all of the cyanide present in the tissue is considerably reduced thereby, and much less foreign volatile organic material passes into the distillate. The latter point is very important, since organic contaminations interfere with the quantitative methods for cyanide.

The organs, as soon as removed from the body, are placed into covered receptacles and then put into the refrigerator. When ice cold, about 125 gm. are passed through a meat grinder that was previously cooled by cracked ice. These precautions are taken in order to prevent any loss of HCN by volatilization. The finely divided tissue (100 gm.) is quickly placed into a 500-cc. flask (Fig. 1, *B*); 300 cc. of cold water, 2 cc. white mineral oil and 10 cc. of 5% tartaric acid are added. The mineral oil prevents frothing during the distillation, and the tartaric acid facilitates the complete removal of the cyanide (HCN). The flask is connected to a vertical, water-cooled condenser (*C*), which in turn is joined to 3 absorption tubes (*D*), connected in series. Each absorption tube contains 10 cc. of N/10 NaOH. Suction is applied to the side-arm of the last absorption tube. The water in the bath (*A*) is heated to boiling. The suction is then regulated so that the content of the flask (*B*) is vigorously agitated, but slowly (about 5 drops per minute) distills into the first alkali absorption tube. Any HCN escaping from tube *D-1* is absorbed in the alkali solutions of *D-2* and *D-3*. After the distillation has run for 2 hours the suction is shut off, and the condenser is disconnected from the distillation

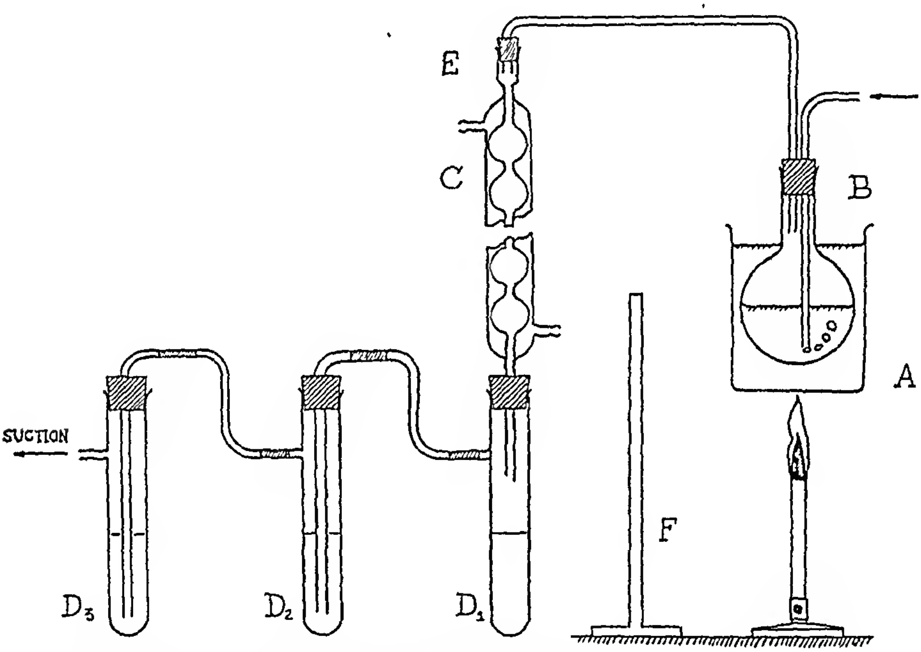

FIG. 1.—*A*, Water bath; *B*, round-bottom flask; *C*, reflux condenser; D_1, D_2, D_3, absorption tubes; *F*, asbestos screen.

flask at *E*. The 3 alkali absorption solutions are quantitatively transferred to a 100-cc. volumetric flask, and the volume then made up to the 100-cc. mark. In case very small quantities of cyanide are suspected in the tissues, this final volume may be easily kept down to 50 cc. by washing each tube successively with the same wash water. If the resulting solution is not perfectly clear, it should be cooled to 0° C. and then filtered through a dry filter paper. Aliquot portions are taken for analysis.

B. DETECTION OF CYANIDE IN HUMAN TISSUES. The following tests have been recommended for the detection of cyanide in gastro-intestinal contents, body tissues and fluids.

1. *Copper-guaiac Test.* Place about 50 gm. of finely ground organ or a few centimeters of stomach contents into a 100-cc. flask. Acidify the material with tartaric acid, and suspend above it a strip of freshly prepared copper sulphate-guaiac paper (filter paper which has been wet in turn with 10% alcoholic solution of guaiac and 0.1% aqueous copper sulphate solution), stopper the flask, warm contents a little and allow to stand about one-half hour. If a blue or green color does not develop on the paper then cyanide is definitely excluded. No further tests for cyanide need be done, because this is the most sensitive test available. If a blue color develops, cyanide may be present. Since, however, the blue color is also produced by ammonia gas, hydrogen chloride, ozone, oxides of nitrogen, bromine, chlorine and hydrogen peroxide, 2 or 3 of the following tests must be resorted to in order definitely to establish the presence of cyanide in the material.

For the following tests, the distillates obtained by steam distillation of the acidified organs and stomach contents are used.

2. *Liebig's Thiocyanate Test.* Twenty cc. of the distillate and 2 cc. of ammonium polysulphide are placed into an evaporating dish, and evaporated to dryness on the steam bath. The residue is treated with 5 cc. of water, then slightly acidified with HCl, warmed a little, thoroughly stirred and allowed to stand several hours, in order that the colloidal sulphur may precipitate. The material is then filtered, and 10% ferric chloride is added dropwise, until a maximum color intensity is obtained. A red color indicates the presence of cyanide.

A variation of the thiocyanate test follows: An aliquot portion of the distillate is boiled with ammonium sulphide for a few minutes, then concentrated to 1 cc., acidified with HCl and extracted several times with ether. The ethereal extracts are allowed to evaporate spontaneously. Dilute ferric chloride solution is added dropwise to the residue as long as the color deepens. If a red color develops, which is soluble in ether, the presence of cyanide is established.

3. *Prussian Blue Test.* Twenty cc. of the distillate are made strongly alkaline with NaOH solution and concentrated to about 2-cc. volume. Two drops of 5% ferrous sulphate and 1 drop of 10% ferric chloride are added, and the mixture is slightly warmed. Concentrated HCl is then added drop by drop (avoid excess), until the brown precipitate (iron hydroxides) just dissolves. If cyanide is present, a deep blue color or precipitate of Prussian blue remains, which is insoluble in dilute HCl.

4. *Vortman Test.* To 5 cc. of the distillate are added a few drops of 10% potassium nitrite solution and 2 to 4 drops of 5% ferric chloride, and sufficient dilute sulphuric acid to give the mixture a bright yellow color. Heat the mixture to boiling, allow to cool, add sufficient ammonia to

precipitate the excess of iron and filter. To the filtrate add a few drops of very dilute ammonium sulphide solution. If cyanide is present, a violet color appears which gradually passes through blue, to green and then yellow.

5. *Phenolphthalein Test.* To 2 cc. of the distillate add 2 or 3 drops of a colorless alkaline solution of phenolphthalein (made by boiling, under a reflux, a dilute NaOH solution of phenolphthalein with zinc dust until colorless) and a drop of very dilute (1 to 2000) copper sulphate solution. The development of a red color indicates the presence of cyanide.

6. *Picric Acid Test.* Five cc. of the distillate are made faintly alkaline with NaOH solution, and 2 or 3 drops of saturated picric acid are added. On warming, a red color develops if cyanide is present in the sample.

7. *Ferrous-uranic Test.* About 5 mg. of ferrous sulphate, and the same quantity of uranic nitrate are dissolved in 50 cc. of water. One cc. of this test solution is placed into a porcelain dish, and 1 or 2 drops of the distillate to be tested are added. The appearance of a gray-purple color, or purple precipitate indicates the presence of cyanide.

8. *Silver Test.* Thirty cc. or less of the distillate are placed into a 50-cc. flask, and acidified with 6N HNO_3. A hanging drop of $AgNO_3$ solution on a glass slide is placed over the mouth of the flask. After 30 minutes the slide is carefully removed, 1 drop of dilute nitric acid is added to the drop on the slide, and a coverslip placed thereon. The material under the coverslip is now slightly heated by playing a very small flame across the under side of the glass slide. On cooling, long slender crystals of AgCN are visible under the microscope. AgCl crystallizes as octahedra, and can therefore easily be differentiated from AgCN.

After many years of experience with the above tests we recommend the use of Test 1 only as a preliminary rapid and sensitive way of ruling out the presence of cyanide. For definitely establishing the presence of cyanide, Tests 2, 3 and 8 give the best and most specific results.

C. QUANTITATIVE METHODS OF ANALYSIS. The various quantitative methods for cyanide described in the literature were critically studied in order to ascertain whether they would yield accurate results when dealing with very small amounts of cyanide (2 to 0.2 mg. per 100 gm.) as found in human organs of fatal cyanide cases.

1. *The Volumetric Silver Nitrate Method* was found to be very accurate for determining small amounts of cyanide ranging between 2 and 0.03 mg. HCN in 25-cc. volume. For values below 0.03 mg. HCN the method gives slightly high results.

2. *The Iodometric Titration* was discarded because (*a*) the reaction with iodine and HCN is reversible; (*b*) starch cannot be used as an indicator, making the end point difficult to observe; (*c*) the reaction upon which the method is based is not specific for the cyanide radicle.

3. *The Colorimetric Method With Picric Acid* is not quantitative. When applied to fresh tissues it yields results that are about 10% too low. With putrefied and embalmed organs the method is entirely valueless. Many volatile substances such as H_2S, SO_2, aldehydes, and so forth, traces of which may be found in tissues, also cause the formation of the red color, and thus interfere. Not-

withstanding its several defects this method can be used as a preliminary, rapid but rough estimation of the cyanide content.

4. *The Colorimetric Method Based Upon the Production of Prussian Blue* was discarded because we found that the intensity of the blue color was not strictly proportional to the cyanide concentration. With large amounts of cyanide the blue precipitate forms, and with low-cyanide concentrations the Fe^{+++} ions impart a green tinge to the blue color (even though KF was added to prevent this) making it impossible to get an accurate reading.

5. *The Colorimetric Method Based Upon the Conversion of the Cyanide to Ferric Thiocyanate* was studied in detail as to the following points: (*a*) To convert completely the cyanide present to thiocyanate by evaporating to dryness with ammonium polysulphide it was found that 10 cc. of ammonium polysulphide must be used for 1 mg. or less of HCN. If the amount of HCN present is much above 1 mg. the conversion to thiocyanate by means of 10 cc. of ammonium polysulphide is not complete. Instead of using more polysulphide, it is better to use an aliquot portion of the distillate containing 1 mg. or less of cyanide. This is approximated by a preliminary determination using the picrate method.

(*b*) Since the reaction for the production of the red color is a reversible one,

$$FeCl_3 + 3HCNS \rightleftarrows Fe(CNS)_3 + 3HCl$$

it is evident that the depth of the red color produced from a definite quantity of HCNS, will also depend upon the amount of Fe^{+++} ions and H^+ ions present. Fe^{+++} ions tend to increase the color, while H^+ ions tend to decrease it. Our experimental results indicated that if the standard thiocyanate solution is near the concentration of the solution to be compared, and if 5 cc. of a 10% $FeCl_3$ solution be added to 50-cc. volumes of each, then the red ($Fe(CNS)_3$) color produced is exactly proportional to the thiocyanate content for values of HCN ranging between 10 and 0.5 mg. in 50 cc. Below 0.5 mg. concentration, the influence of the excess $FeCl_3$ on the color is quite marked. With these low values of cyanide (below 0.5 mg. in 50 cc.) it is therefore especially important to have the standard very close to the value of the solution to be compared.

(*c*) As to the effect of H^+ ions upon the intensity of the red $Fe(CNS)_3$ color, we found that if HCl concentration is kept below 3 cc. of N/10 in 50 cc. of solution, there is no appreciable disturbing effect.

(*d*) Experiments dealing with the stability of the red $Fe(CNS)_3$ color revealed that standing for hours, even in a well-lighted room, had no noticeable effect upon the depth of color.

Our studies revealed that the ferric thiocyanate colorimetric method is very sensitive and accurate, provided the directions as described below are rigidly adhered to.

6. *The Gravimetric Method,* in which the cyanide is weighed as AgCN, was found to be unsuited for the determination of small quantities of HCN in the presence of other volatile organic matter from tissues. The recovery varied between 80 and 200%, and the variation was not constant for any fixed quantity of HCN. The presence of organic reducing substances in the distillate constitutes the chief disturbing factor, this being especially noticeable in cases of putrefaction. The reducing action precipitates some metallic Ag, giving high results. The accurate determination of small quantities of cyanide present in tissues is practically impossible with this method.

Our experiments indicate that of the various quantitative methods for small amounts of cyanide only 2 (silver nitrate titration method and ferric thiocyanate colorimetric method) give accurate results. The colorimetric method with picric acid, although not accurate, is very rapid, and hence of advantage for a rough preliminary estimation of the cyanide content.

D. DETAILED PROCEDURE FOR THE QUANTITATIVE DETERMINATION OF HCN IN TISSUE DISTILLATES. 1. *Colorimetric Method with Picric Acid.* This method simply serves as a rough approximation of the cyanide content.

The tissue is distilled by aëration as has been described above. Ten cc. of the 100 cc. alkaline absorbed distillate (which contains 3 cc. N/10 NaOH) are placed in a 50-cc. flask and 10 cc. of picric acid reagent (0.5% picric acid and 5% Na_2CO_3) are added. The flask is stoppered and contents heated at 50° C. for 1 hour in order to develop the maximum color. When cool again, the red color produced is compared with a standard KCN solution similarly treated. Since alkalinity intensifies the color of the picric acid, it is essential that the standard contain exactly the same amount of alkali as the unknown. The most applicable standard for tissue analysis is made as follows: 60.2 mg. of KCN are weighed out and transferred to a 1-liter flask by means of a little water; 300 cc. of N/10 NaOH, and then enough water is added to bring the volume to exactly 1 liter. Ten cc. of this standard contains 0.25 mg. HCN. In analyzing stomach contents for cyanide, a correspondingly stronger standard should be used.

2. *Colorimetric Ferric Thiocyanate Method.* An accurately measured aliquot of the alkaline absorbed distillate, containing in the neighborhood of 1 mg. of HCN (as previously determined by the picrate method) is placed into a small evaporating dish. Ten cc. of ammonium polysulphide* are added, and the mixture is then evaporated to dryness on the water bath. To the residue are added 30 cc. of water and N/10 HCl until distinctly acid. The mixture is slightly heated, thoroughly stirred, and then allowed to stand overnight to insure complete precipitation of the colloidal sulphur. The mixture is next filtered into a 50-cc. volumetric flask. The evaporating dish and residue on filter paper are washed with small portions of water, and the washings are added to the main filtrate. Five cc. of 10% $FeCl_3$ and enough water are now added to bring the volume to the 50-cc. mark. After thoroughly mixing, the red color obtained is compared in a colorimeter with a standard KCNS solution (3.6 mg. KCNS, equivalent to 1 mg. HCN, plus 5 cc. of 10% $FeCl_3$ made up to 50 cc. with water). Should the HCN content in the distillate be very small (0.2 mg. or less in

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* Saturate 600 cc. of conc. NH_4OH with H_2S, then dilute to 1 liter with conc. NH_4OH. Add an excess of powdered sulphur, and let stand, shaking occasionally, until saturated.

10 cc.) then all working volumes are reduced, and the final volume is kept down to 25 cc.

3. *Volumetric Silver Nitrate Method.* Twenty-five cc. of the alkaline absorbed distillate containing the cyanide are placed into a 50-cc. Erlenmeyer flask; 2 cc. of concentrated NH_4OH and 1 cc. of 10% KI solution are added. The cyanide is titrated with 0.005/N $AgNO_3$ solution. The end point is denoted by the formation of a bluish-white opalescent cloud of AgI. This end point is very sharp, and most easily observed against a black background.

Calculation: each cc. of 0.005/N $AgNO_3$ solution is equivalent to 0.266 mg. of HCN.

In order to compare the accuracy of the 3 methods the following experiments were made. To 100-gm. portions of tissues, known quantities of HCN were added. The tissues were then subjected to distillation as previously described, and the distillates used for the cyanide determination by each of the 3 methods (Table 1).

TABLE 1.—COMPARISON OF RESULTS OBTAINED BY THREE QUANTITATIVE CYANIDE METHODS.

Mg. HCN added to 100 gm. tissue.	HCN recovered.					
	Colorimetric picric acid.		$AgNO_3$ titration.		Colorimetric thiocyanate.	
	Mg.	Per cent.	Mg.	Per cent.	Mg.	Per cent.
50.00	46.80	93.6	49.20	98.4	48.60	97.2
40.00	36.00	90.0	39.00	97.5	39.30	98.2
30.00	27.30	91.0	29.58	98.6	29.37	98.9
20.00	17.55	87.8	19.38	96.9	19.58	97.9
10.00	9.75	97.5	9.84	98.4	9.73	97.3
5.00	4.00	80.0	4.89	97.8	4.82	96.3
1.00	0.89	89.0	0.975	97.5	0.981	98.1
0.50	0.46	92.0	0.475	95.0	0.485	97.0
0.25	0.22	88.0	0.240	96.0	0.240	96.0
0.10	0.08	80.0	0.095	95.0	0.0975	97.5
0.05	0.04	80.0	0.0475	95.0	0.0475	95.0

The results of Table 1 indicate that the colorimetric thiocyanate method and the silver nitrate titration method are fairly accurate. The picric acid method gives low results. Since the latter is a rapid method, however, it can be used to advantage in determining roughly how much cyanide is present. This information is necessary for the proper application of the thiocyanate method.

II. Normal HCN Content of Human Organs. In order to determine whether or not HCN is present in the distillates from fresh normal human tissues, the following experiments were performed: Various body tissues (brain, liver, kidney, lung and blood) were distilled according to the method described above. The entire distillate in each case was then subjected to analysis by the thiocyanate method. This method was chosen because it is the most sensitive. One-hundredth mg. HCN in 100 gm. of tissues (1 part HCN in 10,000,000 parts tissue) can readily be detected. In no case did these experiments show even a trace of HCN. The failure to detect HCN in normal tissues may be interpreted, either that no cyanide whatever is present in normal tissue distillates, or that the minute quantity of cyanide that may be present lies below the sensitivity of the test (0.005 mg. or 5 gamma in 100 gm. of tissue).

III. Distribution of HCN in the Various Body Tissues After Fatal Cyanide Poisoning. Dogs were taken as subjects. Two of the animals were given HCN by inhalation, and 2 KCN solution by stomach tube. The inhalation experiments were carried out with the aid of the apparatus shown in Figure 2.

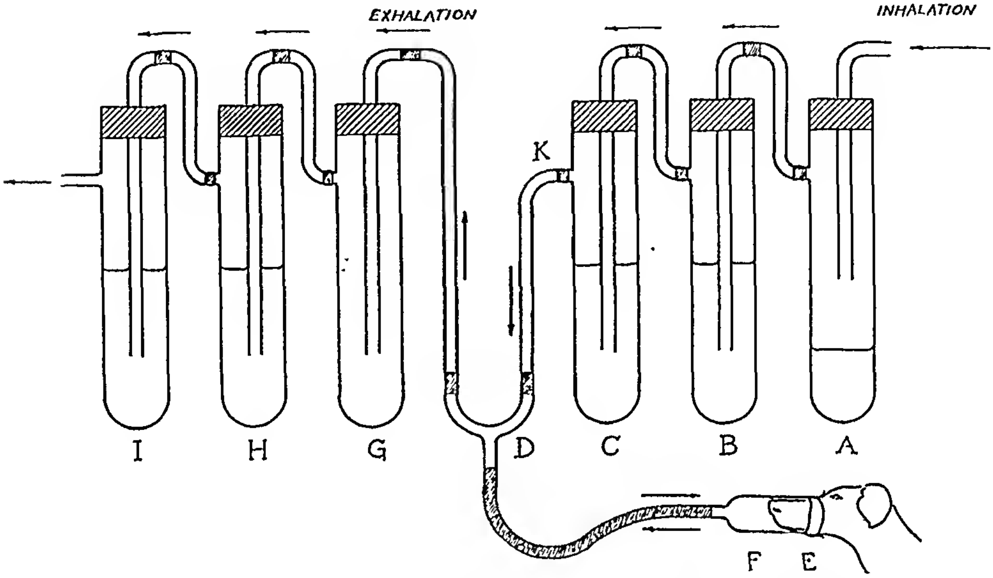

FIG. 2.—*A*, Trap containing sodium hydroxide solution; *B*, acidified potassium cyanide solution; *C*, water; *D*, metal fork; *E*, tape; *F*, large filter tube; *G*, trap; *H* and *I*, one-tenth normal sodium hydroxide solution.

The dog was first securely tied to an ordinary animal operating table, and his jaws were firmly taped, care being taken not to interfere with his breathing. A large filter tube was slipped over his nose and mouth and fastened securely by taping, so as to prevent slipping off during the experiment. The tape was then smeared with vaseline, making it air-tight. As the dog inhaled, the inspired air followed the path pictured in the diagram. First the air bubbled through a solution of HCN (*B*) (known quantity of standard KCN solution acidified with HCl), and then through water (*C*). In this manner the HCN content of the air breathed by the dog was kept fairly low. The expired air, containing any unabsorbed HCN bubbled out through the NaOH solution (*H*) and (*I*), the HCN being absorbed as NaCN. In case of very violent gasping, some of the NaOH may be sucked back, but is then caught in the trap (*G*). At the same time some of the standard HCN solution in (*B*) may be forced back into tube (*A*) containing some NaOH solution. When the dog stopped breathing, the rubber tubing was clamped at (*K*) and gentle suction was applied to exit tube (*I*) for a few seconds. In this manner any HCN remaining in the rubber tubing and other parts of the system is absorbed by the alkali solutions in (*I*) and (*H*). The solutions in tubes (*B*) and (*C*) were now made alkaline with NaOH. Contents of all 6 tubes were quantitatively combined, and made up to a definite volume. The cyanide content was then determined by titration with standard $AgNO_3$ solution. The quantity of HCN absorbed by the dog during the experiment was obtained by subtracting the total cyanide content left in the 6 tubes after the experiment from the amount of cyanide originally placed into tube (*B*).

The various organs and tissues of the dogs were then quantitatively analyzed for the HCN content. All data obtained are charted in Table 2. Data on human Case 15 who had died from inhaling HCN are also presented in this table for purposes of comparison.

TABLE 2.—THE DISTRIBUTION OF INHALED HCN IN BODY TISSUES.

	Dog 1.	Dog 2.	Human Case 15.
Weight (kg.)	10.30	9.10	68.30
Mg. HCN absorbed	16.00	10.10	
Death in	12 min.	8 min.	Found dead
Mg. HCN in 100 gm.:			
Brain	1.08	0.41	0.32
Lungs	2.00	0.88	0.75
Blood	1.71	0.50	0.41
Liver	0.50	0.22	0.21
Kidney	1.00	0.43	0.33
Heart	1.23	0.50	0.42
Stomach wall	0.30	0.10	0.10
Intestinal wall	0.33	0.11	
Muscle	0.29	0.10	
Stomach contents	0	0	0

Dogs 3 and 4 were given KCN solutions by means of a stomach tube. The various organs and tissues of the animals were analyzed for their cyanide content (Table 3).

TABLE 3.—DISTRIBUTION IN BODY TISSUES OF CYANIDE GIVEN PER OS.

	Dog 3.	Dog 4.
Body weight (kg.)	11.90	11.30
Mg. HCN given	100.00	50.00
Mg. HCN left in stomach and intestines	83.40	38.00
Mg. HCN absorbed (by difference)	16.60	12.00
Time until death	8 min.	21 min.
Mg. HCN in 100 gm.:		
Brain	0.50	0.43
Lungs	0.66	0.47
Blood	1.00	0.71
Heart	0.32	0.24
Liver	0.55	0.37
Kidney	0.46	0.38
Muscle	0.19	0.12

During the course of this investigation, 14 human fatal cyanide cases were submitted to us for analysis. In Table 4 are charted the results from 6 of these cases.

TABLE 4.—DISTRIBUTION IN HUMAN ORGANS OF CYANIDE TAKEN PER OS.

Case No.	Tissue analyzed, 100 gm.	Mg. HCN found by $AgNO_3$ titration.	Mg. HCN found by thiocyanate method.	Mg. HCN in 100 gm. tissue.
1	Kidney	0.82	0.82	0.82
	Liver	0.72	0.73	0.73
2	Brain	0.20	0.20	0.20
	Liver	0.21	0.22	0.22
	Kidneys	0.18	0.19	0.19
	Blood	0.76	0.74	0.75
3	Liver	0.66	0.64	0.65
	Stomach contents	76.00	75.40	
4	Brain	0.50	0.51	0.50
	Liver	0.34	0.33	0.33
	Lungs	0.40	0.40	0.40
	Kidneys	0.39	0.39	0.39
	Blood	0.96	1.00	0.98
5	Brain	1.59	1.56	1.37
	Lungs	1.70	1.71	1.70
	Blood	2.06	2.14	2.10
	Liver	0.90	0.92	0.91
	Kidney	0.92	0.90	0.91
	Heart	1.24	1.26	1.25
	Stomach contents	253.00	251.00	
6	Brain	0.06	0.06	0.06
	Liver	0.23	0 21	0.32
	Blood	0.34	0.30	0.32

Glancing over the data of Tables 2, 3 and 4, we notice the following points of interest regarding the distribution of the cyanide in the various organs and tissues of the body:

(*a*) Expressing the results on equal weight basis (100 gm.), the cyanide is quite uniformly distributed in the various internal organs. The blood has a higher concentration (approximately twice that of the organs), while the muscles, stomach wall and intestinal wall have a much lower one (about one-third to one-fourth that of the internal organs).

(*b*) When alkali cyanides are taken by way of the stomach, and death results within 10 to 15 minutes, by far the largest portion (over 70%) of that taken is found in the gastro-intestinal tract. In cases where the cyanide (HCN) has been inhaled, although traces of cyanide were found in the stomach and intestinal walls, no cyanide at all was found in the contents of the stomach and intestines. The lungs of these cases show a relatively higher cyanide content than the other organs. The above points are of value in establishing whether the cyanide was inhaled or ingested.

IV. The Estimation of the Total HCN Present in the Entire Body. In order to determine the total quantity of cyanide present in the entire body, it would be necessary to analyze representative samples of each and every organ, tissue and body fluid. This is usually impossible because 3 or 4 of the internal organs, at the best, are only submitted for analysis. As a result of our studies we believe that a fairly accurate estimate of total amount of cyanide present in the entire body (exclusive of that present in the gastro-intestinal tract) can be obtained from the cyanide content of the brain and liver. In Table 5 we have charted the quantities of cyanide in the entire brain, entire liver and total quantity of HCN that was actually absorbed by our experimental animals (see Tables 2 and 3).

TABLE 5.—RELATIONSHIP OF TOTAL ABSORBED HCN TO THAT PRESENT IN BRAIN AND LIVER.

	Dog 1.	Dog 2.	Dog 3.	Dog 4.
Body weight (kg.)	10.30	9.10	11.90	11.30
Weight of brain (gm.)	90.00	95.00	110.00	105.00
HCN in brain (mg.)	0.98	0.39	0.55	0.45
Weight of liver (gm.)	315.00	320.00	350.00	340.00
HCN in liver (mg.)	1.58	0.87	1.93	1.26
Total HCN in brain and liver (mg.)	2.56	1.26	2.48	1.71
Total HCN absorbed (mg.)	16.00	10.10	16.60	12.00
Ratio: $\frac{\text{Absorbed HCN}}{\text{Brain + liver HCN}}$	6.20	8.00	6.70	7.00

The ratio of total absorbed HCN to total quantity of HCN present in brain and liver (Table 5) is fairly constant, ranging between 6.2 and 8, with an average of 6.97. If, therefore, we multiply the combined amount of cyanide present in the brain and liver by 7, we obtain a fair estimate of the total quantity of absorbed cyanide. This quantity is of course exclusive of that remaining in the gastro-intestinal tract. If it is desired to know the total amount of cyanide in the body, the quantity found in the gastro-intestinal tract must be added to the estimated absorbed amount of cyanide. Since death from cyanide is rapid, the small amount passing into the bladder can be neglected.

TABLE 6.—COMPLETE ANALYSIS OF 3 HUMAN CYANIDE CASES.

	Case 16.		Case 17.		Case 18.	
	Wt. of organ in gm.	Mg. HCN in entire organ.	Wt. of organ in gm.	Mg. HCN in entire organs.	Wt. of organ in gm.	Mg. HCN in entire organs.
Brain	1,320	19.8	1,450	7.3	1,280	3.6
Liver	1,530	13.8	1,800	5.9	1,450	4.2
Kidneys	260	2.4	350	1.4	250	0.5
Heart	300	3.9	380	1.8	280	0.4
Lungs	780	13.3	850	3.4	650	2.6
Spleen and pancreas	260	2.3	320	1.1	190	0.3
Muscles	30,000*	60.0	35,000*	28.0	23,000*	12.5
Gastro-intest. tract (not contents)	1,500	3.3	1,550	1.6	1,150	1.1
Blood	5,000*	105.0	6,000*	48.0	4,500*	31.5
Fat	3,000*	2.2	6,000*	1.2	2,000*	0.6
Bone	12,500*	..	14,000*	..	11,000*	
Skin, hair, nails, etc.	5,000*	..	5,500*	..	4,000*	
Total weights	61,450*	..	73,200*	..	49,750*	
Actual weight of body	62,500	..	74,500	..	50,700	
Remaining tissue by difference	1,050*	2.1*	1,300*	1.3*	950*	0.6*
Total absorbed HCN	..	228.1	..	101.0	..	57.9
Cyanide (HCN) in gastro-intest. tract	..	1222.5	..	455.5	..	238.8
Ratio: $\frac{\text{Absorbed HCN}}{\text{Brain + liver HCN}}$	..	6.8	..	7.6	..	7.4

* Weights that were estimated.

In order to determine whether the total quantity of absorbed cyanide can be estimated from the cyanide content of brain and liver in human cases, we succeeded in obtaining for analysis specimens of practically all of the body tissues in 3 cases of fatal cyanide poisonings (Table 6).

In the 3 cases of Table 6, the total absorbed HCN was obtained from separate analyses of uniform samples of each organ and tissue. The ratio of absorbed HCN to that present in the brain and liver was 6.8, 7.6 and 7.4, respectively, averaging 7.4. These experiments confirmed our findings with the experimental animals, that if the combined cyanide content of brain and liver is multiplied by 7, a fair estimate of the total absorbed amount of cyanide is obtained.

V. The Minimum Lethal Absorbed Dose of Cyanide. The lowest lethal dose of cyanide for an average adult human being has been estimated by various investigators at about 50 to 60 mg. (approximately 1 gr.), calculated as HCN. This figure had no experimental corroboration because it was obtained mainly from the history of the cases. The smallest dose said to have been ingested and known to have produced death was taken as the lethal dose. Our experimental results prove that most of the ingested cyanide is not absorbed into the body proper, but is found in the gastro-intestinal tract after death. That portion of the poison remaining in the gastro-intestinal tract has no bearing on the death. In order to arrive at a fair estimate for the minimum lethal absorbed dose of cyanide, we present some of our experimental results in Table 7;

TABLE 7.—DATA ON MINIMUM LETHAL ABSORBED DOSE.

	Body wt., kg.	Cyanide given mg. HCN.	Given by.	Time (in min.) until death.	Mg. HCN absorbed.	Mg. HCN absorbed per kg.	Per cent HCN absorbed.
Dog 1 . . .	10.3	16.0	Inhalation	15	16.0	1.55	100.0
Dog 2 . . .	9.1	10.1	Inhalation	10	10.1	1.11	100.0
Dog 3 . . .	11.9	100.0	Stomach	8	16.6	1.40	16.6
Dog 4 . . .	12.7	20.0	Stomach	155	14.4	1.14	72.0
Dog 5 . . .	11.3	50.0	Stomach	21	12.0	1.06	24.0
Human Case 16	62.5	Estim. as 1450.6	Stomach	Found dead	228.1	3.60	15.7
Human Case 17	74.5	Estim. as 556.5	Stomach	Found dead	101.0	1.40	18.1
Human Case 18	50.7	Estim. as 296.7	Stomach	Found dead	57.9	1.10	19.5
Human Case 19	51.0	Estim. as 29.8	Stomach	180	24.4	0.54	81.9

Data in Table 7 were obtained from experimental results presented in Tables 2, 3 and 6. Human Case 19 was found in a ladies' rest room in coma and died 3 hours later. Chemical analysis revealed the presence of cyanide in the following amounts (calculated as HCN): Brain, 0.8 mg. in 1250 gm.; liver, 3.1 mg. in 1450 gm.; blood, 11.7 mg. in 4500 cc.; gastro-intestinal contents complete, 5.4 mg. From the total amount of cyanide found in the brain and liver, it was estimated that the total amount of absorbed HCN present in the body at the time of death was 24.4 mg. (0.48 mg.

per kilo). The total quantity of cyanide taken was estimated to be 29.8 mg. (calculated as HCN), because only 5.4 mg. were found left in the entire gastro-intestinal tract. Investigation seemed to show that this was a suicide; it is therefore difficult to understand why so little cyanide was taken.

The data of Table 7 reveal the following interesting points:

(*a*) The average absorbed lethal dose of cyanide, found at time of death is 1.4 mg. HCN per kilo of body weight.

(*b*) The larger the dose that is taken the sooner does the absorbed HCN reach this figure of 1.4 mg. per kilo, and therefore death ensues in a few minutes. If the dose taken is relatively small, it takes a much longer time until the fatal dose of 1.4 mg. per kilo is absorbed, and the time until death is therefore prolonged. With very small doses (Dog 5) 2 hours and 35 minutes elapsed before death. In human Case 19, who evidently took a very small dose, death set in only after about 3 hours.

(*c*) The minimum lethal absorbed dose of cyanide (human Case 19) is 0.5 mg. HCN per kilo of body weight.

VI. Symptoms of Cyanide Poisoning. In acute cyanide poisoning the victims collapse suddenly, with or without convulsions, and death results in 2 to 5 minutes. With relatively smaller doses (50 to 100 mg. of KCN) even 10 minutes may elapse before symptoms of staggering, palpitation, dyspnea, feeling of oppression in chest, and dilated pupils are observed. Death results after 20 minutes to 1 hour. In 1 of our cases, in which it was estimated that as little as 30 mg. HCN had been taken, 3 hours elapsed before death.

VII. Methylene Blue as a Cyanide Antidote. The following experiments were performed to test the value of methylene blue as an antidote for cyanide poisoning. Three dogs were injected intravenously with 20 cc. of 1% methylene blue, and then given known amounts of cyanide by stomach tube (Table 8). Data on 2 control dogs that were given cyanide but no methylene blue are also given.

TABLE 8.—METHYLENE BLUE AS A CYANIDE ANTIDOTE.

	Dog 3 (control).	Dog 6.	Dog 4 (control).	Dog 7.	Dog 8.
Body weight	11.90	13.90	11.30	12.10	9.70
Meth. blue (1% sol.) (cc.)	None	20.00	None	20.00	20.00
Mg. HCN given	100.00	100.00	50.00	50.00	50.00
Mg. HCN left in gastro-intest. tract	83.40	29.90	38.00	2.40	6.80
Mg. HCN absorbed (by difference)	16.60	70.10	12.00	47.60	43.20
Time (in min.) until death	8	65	21	180	135
Mg. HCN in 100 gm.:					
Brain	0.50	0.52	0.43	0.08	0.37
Lungs	0.66	1.32	0.47	0.13	0.52
Blood	1.00	1.89	0.71	0.19	0.91
Liver	0.55	1.10	0.37	0.10	0.46
Kidney	0.46	1.21	0.38	0.18	0.43
Heart	0.32	1.18	0.24	0.11	0.37
Muscles	0.19	0.21	0.12	0.06	0.12

Data in Table 8 reveal two very interesting points: (*a*) In the presence of methylene blue the lethal quantity of absorbed cyanide is much higher; (*b*) methylene blue is of definite value in at least prolonging life for an hour or more in cases of cyanide poisoning. Should this treatment be supplemented by a stomach lavage, artificial respiration, and injection of stimulants, followed by a second injection of methylene blue if the subject shows a return to unfavorable symptoms, there is a chance of recovery, provided the treatment is instituted as soon as the cyanide has been taken.

VIII. Treatment of Cyanide Poisoning. Treatment is rarely possible, because death occurs so rapidly. Quick action is therefore essential. When the poison was taken by mouth, attempt a thorough removal of the poison from the stomach by means of stomach pump, and then by oxidation with 3% hydrogen peroxide or 0.2% potassium permanganate solution. At the same time, a second operator should give methylene blue intravenously (1 cc. of 0.1% Merck's medicinal methylene blue in Ringer solution per kilo of body weight). Keep the respiration and circulation going by artificial respiration and injections of lobeline, with cardiazole.

IX. Effect of Putrefaction on the Cyanide Content of Tissue. The cyanide content of the organs from cyanide poisoning cases autopsied on the day of death was accurately determined. Portions of these same organs were then placed in receptacles, and were allowed to stand at room temperature for periods ranging between 7 to 28 days. During this time putrefaction developed to a high degree. The putrefied organs were then again analyzed for their cyanide content. We found that putrefactive substances interfere in the colorimetric picrate method and in the silver nitrate titration. The colorimetric thiocyanate method alone gives reliable results when applied to putrefied material (Table 9).

TABLE 9.—EFFECT OF PUTREFACTION OF PRE-EXISTING CYANIDE IN TISSUE.

Case No.	Tissue used.	Time of putrefaction, days.	Mg. HCN present originally.	Mg. HCN found.	% HCN destroyed.
1	Brain	7	0.20	0.18	5.0
2	Liver	14	3.12	3.01	3.5
3	Liver	21	1.58	1.48	6.6
4	Liver	28	0.47	0.42	10.6

Data in Table 9 indicate that the cyanide content of tissues is but little changed during putrefaction. The loss of cyanide after 28 days of intense putrefaction amounts to only about 10% of the amount of cyanide originally present in the tissue.

X. Is Cyanide Produced During Putrefaction of Normal Tissue? The question as to the formation of cyanide during tissue putrefaction may be an important one in medico-legal work. The following experiments were conducted in order to determine whether cyanide was produced during putrefaction and if so, how much.

Eight specimens of brain and liver tissue were weighed out, placed in glass flasks, and tightly sealed. The flasks were allowed to stand in the laboratory at room temperature. At various intervals (see Table 10) the putrefied specimens were distilled, and the distillates analyzed for cyanide, using the colorimetric thiocyanate method. The picric acid method and the silver nitrate titration method could not be used, due to the interfering action of volatile sulphides and other putrefactive products present in distillates from the putrefied material. The experimental results are given in Table 10.

TABLE 10.—CYANIDE PRODUCTION DURING TISSUE PUTREFACTION.

Gm. tissue used.	Length of putrefaction, days.	Mg. HCN found.	Mg. HCN found per 100 gm. tissue.
500	0	0.00	0.000
550	1	0.10	0.018
475	3	0.11	0.023
470	5	0.14	0.029
533	7	0.16	0.030
415	14	0.13	0.031
520	21	0.12	0.023
588	28	0.09	0.015
486	2 mos.	0.05	0.010

In order to confirm the actual presence of cyanide the following test was conducted: 30-cc. portions of several of the distillates were placed in 150-cc. Erlenmeyer flasks, and acidified with 6N. HNO_3. A hanging drop of $AgNO_3$ solution on a glass slide was placed over the mouth of the flask so that it came in contact with the rising vapors from the acidified distillate. The drop of $AgNO_3$ solution gradually darkened. After about 30 minutes the slide was carefully removed. To the blackened drop of silver nitrate solution was added a drop of dilute nitric acid. A cover glass was placed upon it. The material under the cover glass was now slightly heated by playing a very small flame across the under side of the glass slide. A clear solution resulted from which crystals appeared on cooling. When examined under the microscope, long slender crystals of AgCN were found. These crystals showed characteristic parallel extinction when placed in polarized light and rotated.

The experimental results charted in Table 10 indicate that small traces of cyanide are produced during the tissue putrefaction (0.01 to 0.03 mg. of HCN per 100 gm. of tissue). The cyanide content increases during the first 7 days but thereafter it gradually decreases, and after 2 months the cyanide content is only just about within the sensitivity of the test. The highest cyanide content produced by putrefaction (0.03 mg. in 100 gm. tissue) is approximately only one-tenth of the lowest content ever found in organs where death was due to cyanide poisoning. Putrefaction therefore should in no way interfere in deciding a cyanide poisoning case.

XI. Effect of Embalming Upon the Cyanide Content of Organs. Another question having an important medico-legal aspect is the effect of embalming upon the cyanide content of tissue. To throw some light upon this problem the following experiments were performed: 500-gm. portions of brain and liver tissue were placed in each of 8 Erlenmeyer flasks. To each of the 8 samples known amounts of cyanide and 20 cc. of undiluted embalming fluid were added and thoroughly mixed. It was estimated that 20 cc. of the fluid was approximately present in the brain after a typical embalming. At intervals, indicated in Table 11, the embalmed tissues were distilled and analyzed. For the analysis by the $AgNO_3$ titration method, an excess of NH_4Cl was added to an aliquot portion of the distillate and allowed to stand overnight. This results in the conversion of the formaldehyde to hexamethylene tetramine, which then does not interfere in the titration. The remainder of the distillate was analyzed by the colorimetric thiocyanate method. The results of the analyses are given in Table 11.

TABLE 11.—EFFECT OF EMBALMING ON THE CYANIDE CONTENT OF TISSUES.

500 gm. tissues + 50 mg. HCN + 20 cc. embalming fluid.

Analysis made after, days.	Mg. HCN found.	% HCN removed by embalming.
(A)		
3	0.66	98.7
5	0.53	98.9
7	0.25	99.5
14	0.05	99.9
(B)		
3	7.00	98.6
5	4.50	99.1
7	2.50	99.5
14	0.50	99.9

From the results presented in Table 11 it is evident that cyanide (HCN) in tissues is rapidly lost when the tissue is embalmed with solutions of formaldehyde. After only a 3-day period, the HCN content is reduced to about one-hundredth of the original amount. With such a low cyanide content the Prussian blue test may result negatively (not being as sensitive as the thiocyanate test) and hence the presence of cyanide might easily be overlooked. If quantities of cyanide around 500 mg. are present, as are usually found in the stomach contents, then detection is possible up to 7 days of contact with embalming fluid. Longer contact (14 days) reduces the cyanide content to very low values (0.1 mg. HCN in 100 gm.), making the detection of cyanide difficult even in the stomach contents.

Summary. The following phases of cyanide poisoning have been studied, and are discussed in detail:

1. Analytical methods for the detection and quantitative estimation of cyanide in tissues.
2. The normal cyanide (HCN) content of human organs.

3. The distribution of cyanide in the various organs, after fatal cyanide poisoning.
4. A method for estimating the total amount of cyanide present in the entire body after fatal cyanide poisoning.
5. The minimum lethal absorbed dose of cyanide.
6. Symptoms of cyanide poisoning.
7. Methylene blue as an antidote for cyanide poisoning.
8. The treatment of cyanide poisoning.
9. Effect of putrefaction on the cyanide content of human organs.
10. The production of cyanide during the putrefaction of human organs.
11. The effect of embalming upon the cyanide content of human organs.

HISTOPATHOLOGIC STUDY OF TISSUES OF 65 PATIENTS INJECTED WITH THORIUM DIOXIDE SOL FOR HEPATOSPLENOGRAPHY.

WITH A FOLLOW-UP STUDY OF 10 OLD CASES.

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THE use of thorium dioxide sol has not been received with favor by most clinicians for use in patients as a roentgenographic contrast medium because: 1, This substance once injected into the blood stream is retained for years in the reticulo-endothelial cells of the body; 2, it possesses some radioactivity; and 3, there is a possibility that it may be productive of malignant growth of cells when injected into the subcutaneous tissues. In 1932, the Council on Pharmacy and Chemistry of the American Medical Association[3] reported unfavorably on its use in man. In 1937, an editorial appeared in the *Journal of the American Medical Association*[1] urging great caution in its use. Taft[6] has recently discussed the subject of the radioactivity of the substance in the tissues, showing by means of the Geiger counter that one clinical dose (75 cc.) gives the gamma ray activity equivalent to 1.37 micrograms of radium, a figure in close accordance with that stated in the report of the Council on Pharmacy and Chemistry. As little as 2 micrograms of radium has produced symptoms of radium poisoning.

Thus far definite permanent harmful effects due to its use in man have not been demonstrated to our satisfaction, but those working with animals have repeatedly shown potentialities for harm in laboratory experiments.

We have never maintained that the use of thorium dioxide is entirely harmless, but in an experience involving several hundreds of patients over a period of 6 years we have not observed any permanent harmful effects and extremely few immediate alarming reactions. Because of the slowness with which the effects of radioactive substances develop, several years more must elapse before it may be said that the use of thorium dioxide sol in the amounts used is or is not harmless. Until such time, caution should be observed in its use, small doses only being employed, as for arteriography, or larger doses for hepatosplenography being used only in those patients whose span of life is probably limited to a few years.

It is the purpose of this communication to report a follow-up study of 10 patients who received intravenous injections of thorium dioxide for hepatosplenography several years ago and to demonstrate the fate of the substance in the tissues of 65 patients on whom biopsies or necropsies were performed.

Although thorium dioxide sol has been used as a contrast medium for many purposes, it is used in largest amount for hepatosplenography. The preparation we have used in all our cases has been a stabilized colloidal solution of thorium dioxide containing approximately 22% of metal by volume.* This substance when injected into the blood stream is rapidly removed and engulfed by the reticulo-endothelial cells throughout the body. These cells, being most numerous in the liver and spleen, allow these organs to be demonstrated on Roentgen ray films, because thorium, a metal of high atomic weight, is radiopaque. The average dose employed by us has been 75 cc., being given usually in divided doses of 25 cc. on successive days. This amount of the solution contains a quantity of thorium dioxide equivalent in alpha ray activity to from 1.5 to 3 micrograms of radium. The beta ray and gamma ray activity is probably insignificant. The uses of hepatosplenography have been reviewed by Yater, Otell and Hussey (1936)[7] in a report of a follow-up study of 200 patients examined over a period of 5 years, and we shall not discuss the value of hepatosplenography in this paper. These authors also described the roentgenographic changes occurring in the liver and spleen in the first few years following the administration of thorium dioxide.

I. **Follow-up Study of Ten Patients.** CASE 1.—Miss M. B. C., now aged 65 years, was found to have chronic lymphatic leukemia in July, 1930. The first hepatosplenogram was made on July 16, 1931, following the injection of 60 cc. of Thorotrast. Roentgen ray therapy caused the blood picture to return to normal, and she has required such therapy only once since then. She has remained well for nearly 6 years to date (June 1, 1937) with only an occasional upper respiratory infection and minor complaints. Some of the Thorotrast was injected accidentally in the subcutaneous tissues of both arms, causing nodular swellings. These are firm and unsightly but the patient refuses to have them excised. They have not enlarged. The original hepatosplenogram showed some enlargement of the liver and moderate enlargement of the spleen. The last film, made on January 11, 1937, shows the liver to be somewhat smaller, homogeneous, but of moderately reduced density. The spleen is also somewhat smaller and less dense. A small lymph node containing Thorotrast is visible on the right side of the first lumbar vertebra; it was first observed in April, 1935.

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* The preparation employed was Thorotrast, manufactured by the Heyden Chemical Corporation of New York.

Case 2.—Mrs. I. D., now aged 55, had hepatitis with severe jaundice for several weeks in November, 1931. Biopsy of the liver showed a chronic fibrosing process with a superimposed acute one characterized by large areas of leukocytic infiltration. A bromsulphthalein test of liver function after recovery from the acute hepatitis showed 50% retention after 5 minutes and none at the end of 30 minutes. On February 4, 1932, after injection of 60 cc. of Thorotrast, hepatosplenograms showed the liver to be quite small, the medium well concentrated, and no apparent alteration of structure. The left lobe was large, compared with the right. The spleen was normal in size and density. Except for various intermittent complaints, such as dyspepsia and headaches and a rare "cold," she has been well, and physical examination on May 24, 1937, was essentially negative. A liver function test performed on October 10, 1936, gave results identical with the original one. The last hepatosplenogram, made May 24, 1937, more than 5 years after the first, shows the liver and spleen to be about the same size as originally but there is great mottling and moderate reduction in density of both organs, indicative of elimination of the contrast medium, and very dense shadows of upper abdominal lymph nodes to which the mobilized Thorotrast has migrated (Fig. 1).

Case 3.—M. A., a white woman now more than 33, had a prolonged illness in the fall of 1931 accompanied for a while with severe jaundice and ascites which gradually disappeared. Biopsy of the liver showed a subacute inflammatory process. After recovery, the bromsulphthalein test showed 75% retention in 5 minutes and 15% in 30 minutes. Hepatosplenograms made, December 10, 1931, after injection of 60 cc. of Thorotrast, showed the liver and spleen to be of normal size, but the liver was finely mottled. The patient has been well except for minor ailments. Physical examination on April 2, 1937, was essentially negative. She had gained 20 pounds. The liver function test showed 35% retention in 5 minutes and none after 30 minutes. The hepatosplenogram, nearly 5½ years after the first, shows linear and granular mottling of the liver and spleen, indicative of mobilization of Thorotrast, and visible lymph nodes between the two organs.

Case 4.—Mr. F. S., aged 42, was found to have diabetes mellitus in 1931. Dietetic treatment caused carotinemia. Hepatosplenograms made on February 6, 1932, after injection of 75 cc. of Thorotrast, showed normal hepatic and splenic shadows. The patient has been very well. Hepatosplenograms made on May 24, 1937, more than 5 years after the first, show some diminution in density and mottling of the liver and spleen, and lymph nodes are visible in the upper abdomen.

Case 5.—Miss L. B., aged 13, was run over by an automobile on November 30, 1932, resulting in shock and severe pain in the upper left quadrant of the abdomen. To determine whether the spleen was ruptured 8 cc. of Thorotrast was injected and a hepatosplenogram made 3 hours later. This showed the spleen to be intact. Recovery ensued without a surgical

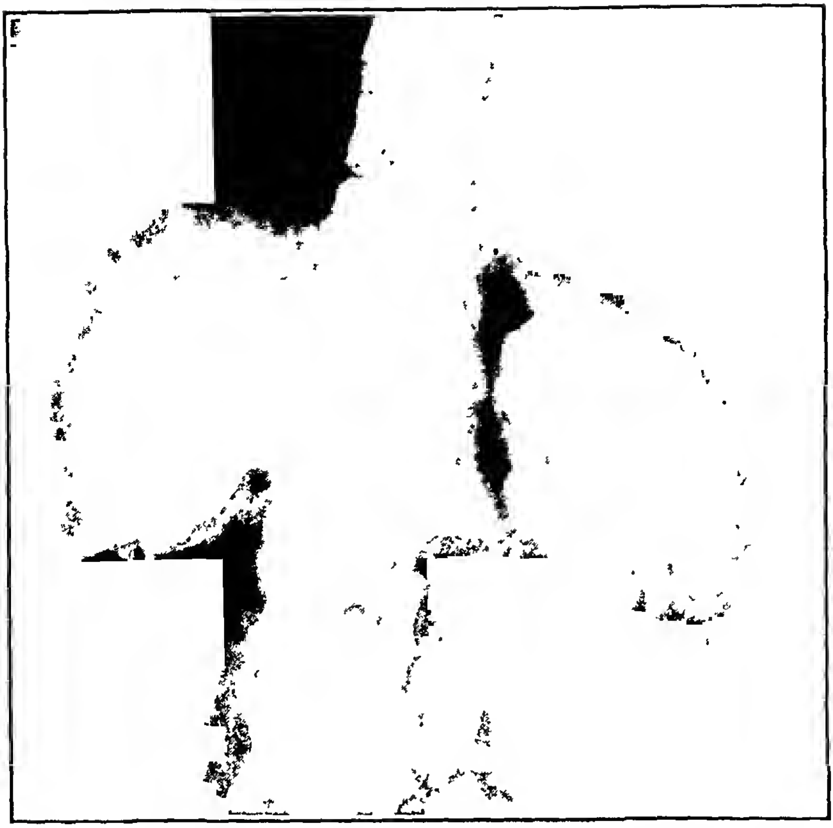

Fig. 1.—(Case 2.) Hepatosplenogram made more than 5 years after injection of 60 cc. of Thorotrast in a case of cirrhosis of the liver, showing the rather small right lobe and the enlarged left lobe of the liver which is mottled because of mobilization of Thorotrast. The spleen is not enlarged but is mottled. A large group of lymph nodes containing Thorotrast is demonstrable anterior and to the right of the spine.

Fig. 2.—(Case 6.) Hepatosplenogram made on March 22, 1932, after injection of 75 cc. of Thorotrast, showing enlarged, lobulated and mottled liver (hepar lobatum) with splenomegaly.

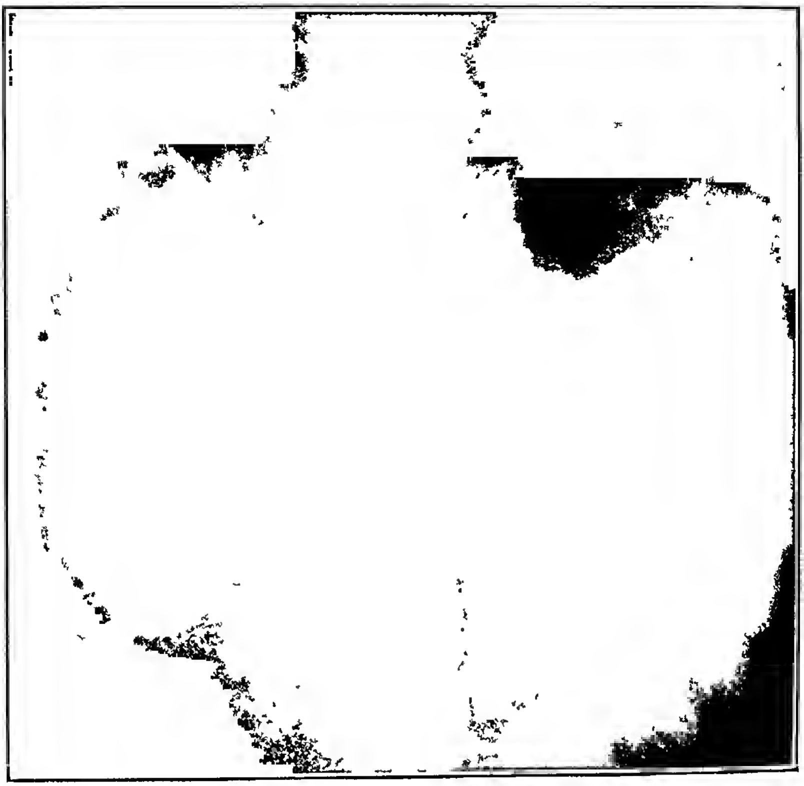

Fig. 3.—(Case 6) Hepatosplenogram made on May 19, 1937, showing gross and irregular mottling of the liver due to the mobilization of Thorotrast. Many lymph nodes containing the mobilized Thorotrast are visible. Spleen still enlarged and still quite dense.

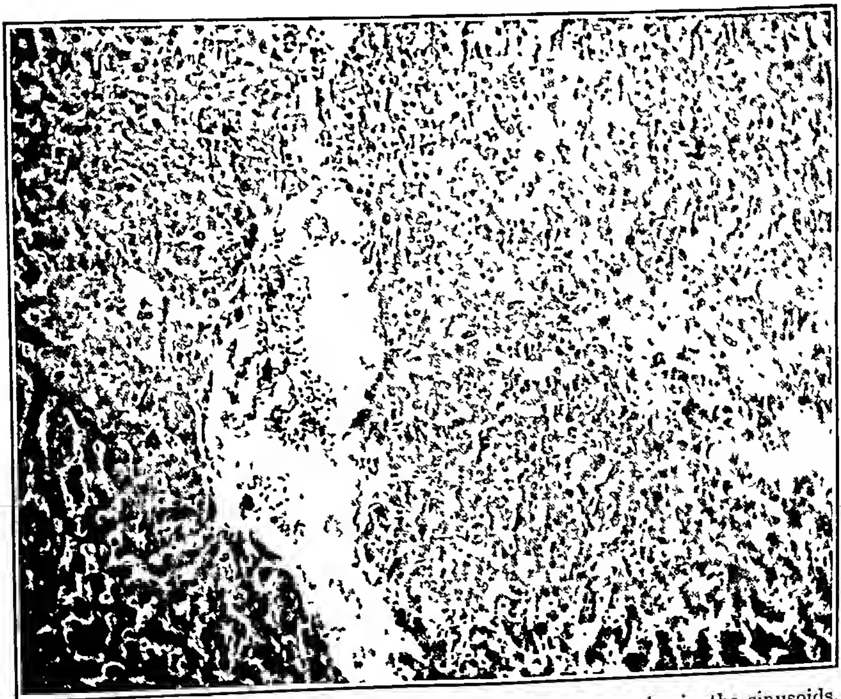

Fig. 4.—(Case 11.) Section of liver, showing masses of granules in the sinusoids, with no concentration about the central veins or in the portal areas.

operation. The patient has remained well and developed normally. A hepatosplenogram made on May 3, 1937, 4½ years after the first, shows very dim shadows of the liver and spleen with diffuse granular mottling of the latter and visible lymph nodes near the porta hepatis. Some Thorotrast had been accidentally injected into the subcutaneous tissues of both arms and small firm nodules had resulted. These did not cause trouble and were painful only when the arm was squeezed. One was removed for microscopic study (see below).

CASE 6.—Mrs. D. M., aged 41, was found to have syphilis 17 years ago, and treatment has been given intermittently therefore. Dyspepsia developed, and in January, 1931, the liver and spleen were found to be enlarged. In October, 1932, the liver was considerably enlarged, firm and irregular; the spleen was also moderately enlarged. A bromsulphthalein test showed 45% retention at the end of 5 minutes and none after 30 minutes. Hepatosplenograms made on March 22, 1932, after the injection of 75 cc. of Thorotrast, showed the typical picture of hepar lobatum with splenomegaly (Fig. 2). In October, 1935, she delivered a normal baby. She has been working since then, but she has frequent nosebleeds and tires easily. On May 19, 1937, the physical examination was essentially the same as in 1932. The liver function test showed 50% retention after 5 minutes and 5% after 30 minutes. Wassermann and Kahn tests of the blood were strongly positive. The hepatosplenogram made more than 5 years after the first shows extensive, irregular coarse mottling of the liver due to mobilization of the contrast medium, many visible lymph nodes in the upper abdomen, and still considerable density of the enlarged spleen (Fig. 3).

CASE 7.—Mrs. G. B., aged 65, had a severe attack of jaundice in April, 1932. Cholecystostomy was performed, followed by recovery. A hepatosplenogram, made May 7, 1932, after injection of 75 cc. of Thorotrast, showed normal hepatic and splenic shadows. The patient has been well since then except for minor ailments, although the bromsulphthalein test has always shown some impairment of hepatic function. The last hepatosplenogram, made April 30, 1937, practically 5 years after the first, shows some diminution in density of the liver and spleen with mottling and visible lymph nodes in the upper abdomen.

CASE 8.—J. C., a negress, aged 32, was found to have chronic myeloid leukemia in August, 1933. Her highest leukocyte count was 385,000 per c.mm. of blood. A hepatosplenogram made September 9, 1933, after injection of 75 cc. of Thorotrast, showed enlargement of the spleen which was considerably less dense than normal. The liver although of normal size was also less dense than normal. The patient has received Roentgen ray treatment at intervals and has been fairly well until lately, when severe pains in the back and thighs have developed. The spleen has been practically impalpable. A hepatosplenogram made, June 3, 1937, nearly 4 years after the first, shows the spleen to be only slightly enlarged; there is mottling of both liver and spleen, and upper abdominal lymph nodes are visible.

CASE 9.—E. C., a white boy, aged 8, was found to have xanthomatosis in 1931. A hepatosplenogram made on March 24, 1932, after injection of 25 cc. of Thorotrast, showed normal shadows for liver and spleen. Under Roentgen ray therapy he has improved greatly. A hepatosplenogram made on December 19, 1936, nearly 5 years after the first, showed considerable diminution in density of the liver and spleen with mottling and visible upper abdominal lymph nodes. The liver function test is normal.

CASE 10.—R. W., a white girl, aged 14, had purpura hæmorrhagica in March, 1932. A hepatosplenogram made on March 20, 1932, after injection of 25 cc. of Thorotrast, showed apparently normal liver and spleen. The patient has been quite normal since then. A hepatosplenogram made on July 8, 1936, more than 4 years after the first, shows considerable diminution in density with mottling of the liver and spleen and a visible lymph node near the porta hepatis.

Summary of Follow-up Study of Patients. 1. Ten patients have been reported from among a large number of patients still alive years after the injection of Thorotrast for the making of hepatosplenograms. These 10 patients have lived from nearly 4 to nearly 6 years after the injection of the contrast medium. Some of the patients have very serious diseases, such as leukemia and cirrhosis of the liver, but all are doing as well or better than patients with similar diseases. In 2 patients subcutaneous nodules resulted from the accidental injection of Thorotrast into the tissues of the arm, but there is no evidence of neoplastic reaction adjacent to the nodules.

2. The liver and spleen still cast excellent shadows in all, but there is evidence in all of mobilization of the Thorotrast from these organs in varying degrees, with evidence also of deposition of the contrast medium in adjacent lymph nodes.

II. **Histopathologic Study.** When any foreign substance remains in the tissues for a long time, we must consider possible injury to the tissues. Certain inert substances, as carbon, have little or no injurious action on the tissues; others, as silicates, have a decidedly injurious action on the tissues. Of outstanding interest at present is the action of certain specific carcinogenic substances obtained from coal tar, such as dibenzanthracene. The specificity of these various injurious agents is of great importance.

It is well known that radioactive substances have an injurious action on the tissues. The radioactive ores of the Schneeberg and Joachimsthal mines are known to produce bronchogenic carcinoma; necrosis and sarcoma of the bones in watch-dial painters is another familiar example.

Undoubtedly there is a potential danger in the injection of thorium dioxide into the tissues. Taft[6] has measured the radioactivity of thorium dioxide sol, in terms of gamma rays; a number of workers have considered the formation and retention of degradation products of thorium which emit alpha rays that are very toxic to tissues. And there are numerous reports of animal experimental work, in which damage was done to the tissues by injected Thorotrast.[1,2,4,5]

With this evidence of the potential danger of the diagnostic injection of thorium dioxide before us, it is important to study the actual danger by examination of the tissues of patients who have received such injections. Two factors have to be considered: length of time after the injection and the condition for diagnosis of which the injection was made. Time is the more important factor since neoplastic reaction and the effects of radioactivity are not expected to occur until long—years—after the material is injected.

We are making such studies, and this report is based on some of the cases in this study. The illustrative cases have been chosen on

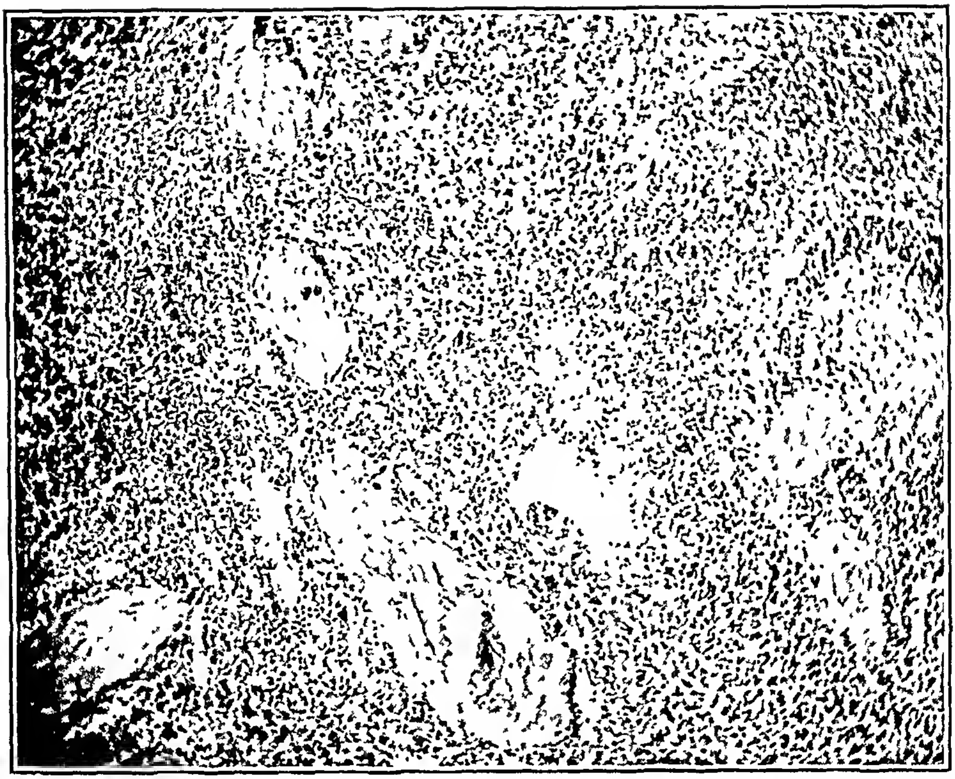

Fig. 5.—(Case 11.) Section of spleen, showing masses of granules distributed through the pulp, none in the Malpighian corpuscles, and no special accumulation about the trabeculæ.

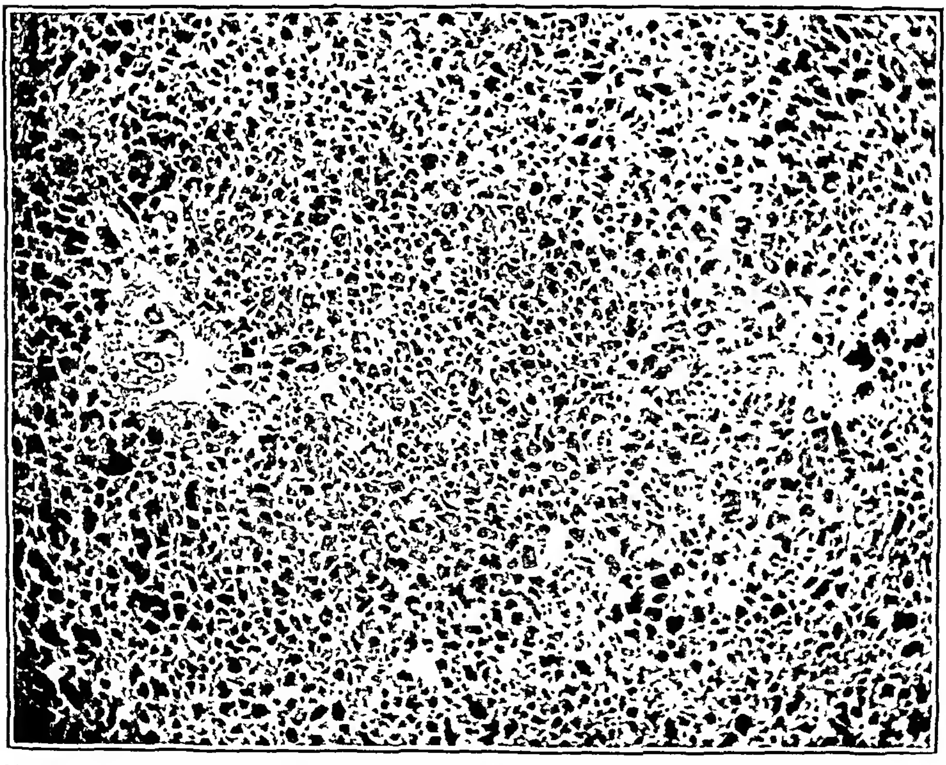

Fig. 6.—(Case 12.) Section of liver, showing masses of granules in the sinusoids, with no accumulation about the central veins or in the portal areas.

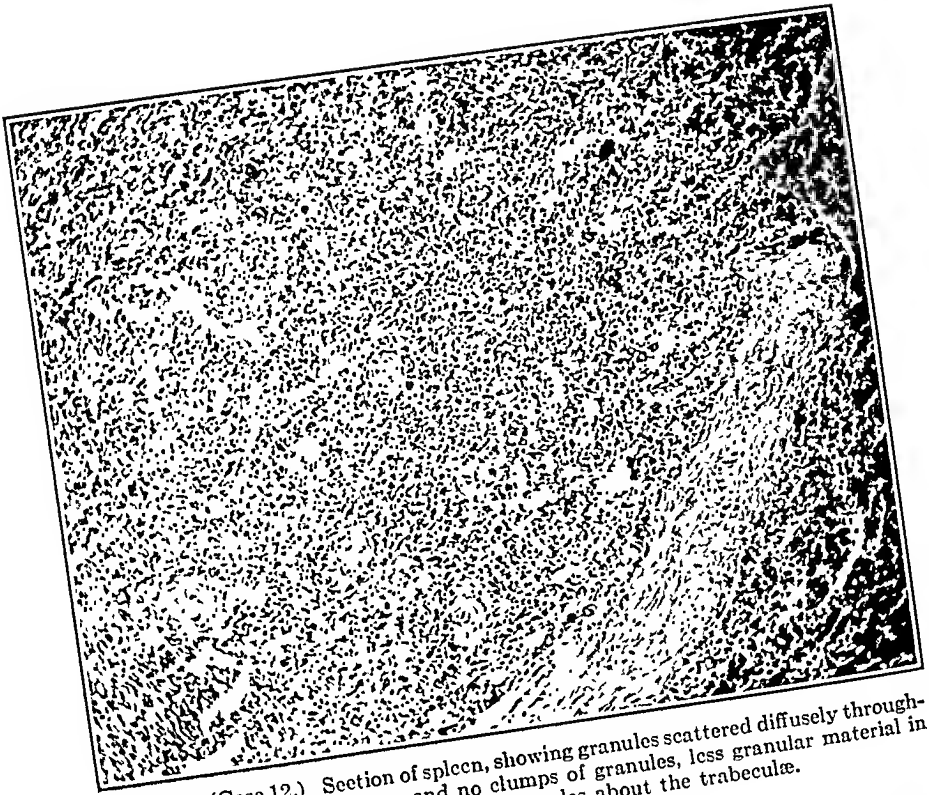

Fig. 7.—(Case 12.) Section of spleen, showing granules scattered diffusely throughout the pulp, with few masses and no clumps of granules, less granular material in the corpuscles, and no accumulation of granules about the trabeculæ.

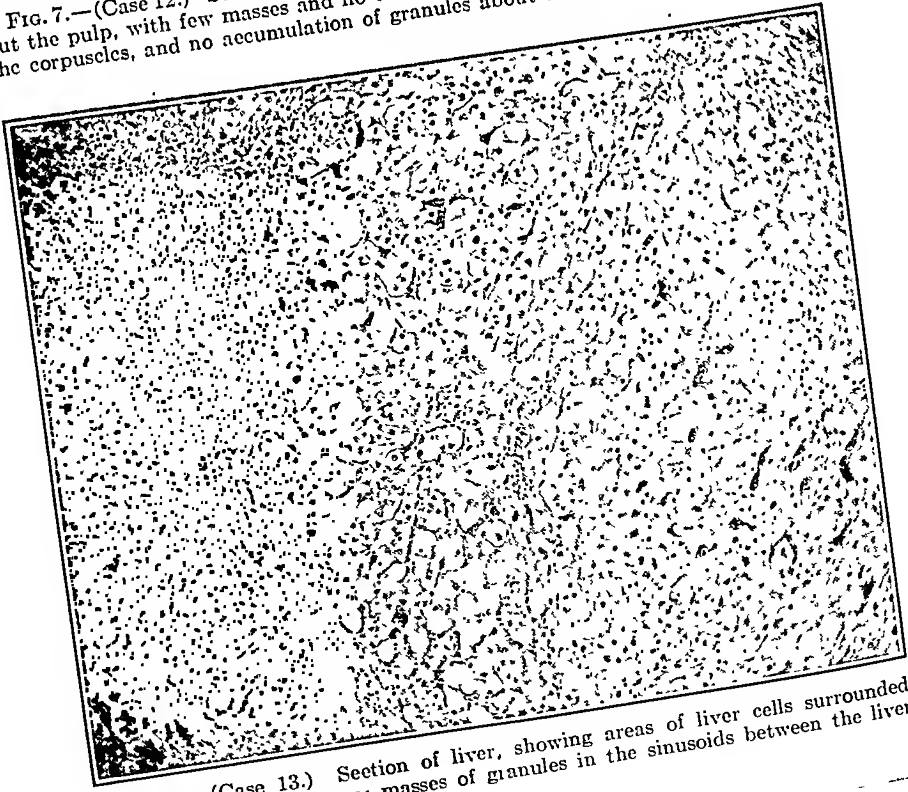

Fig. 8.—(Case 13.) Section of liver, showing areas of liver cells surrounded by bands of fibrous tissue; masses of granules in the sinusoids between the liver cells.

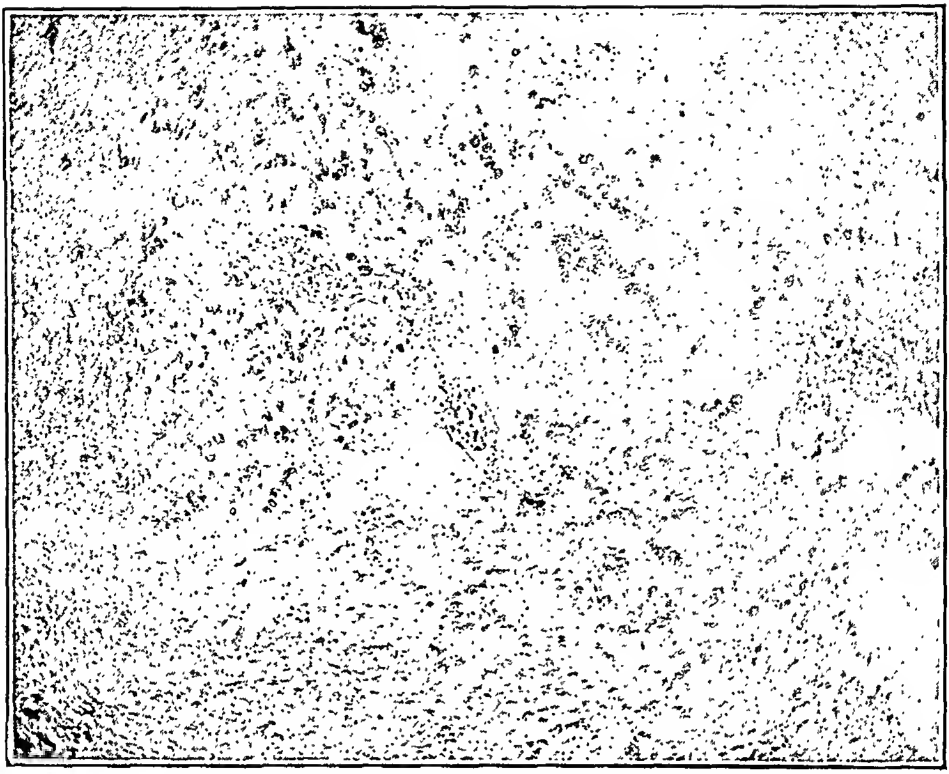

Fig. 9.—(Case 13.) Section of spleen, showing abundant masses of granules throughout the pulp, very little in the corpuscles and no accumulation about the trabeculæ.

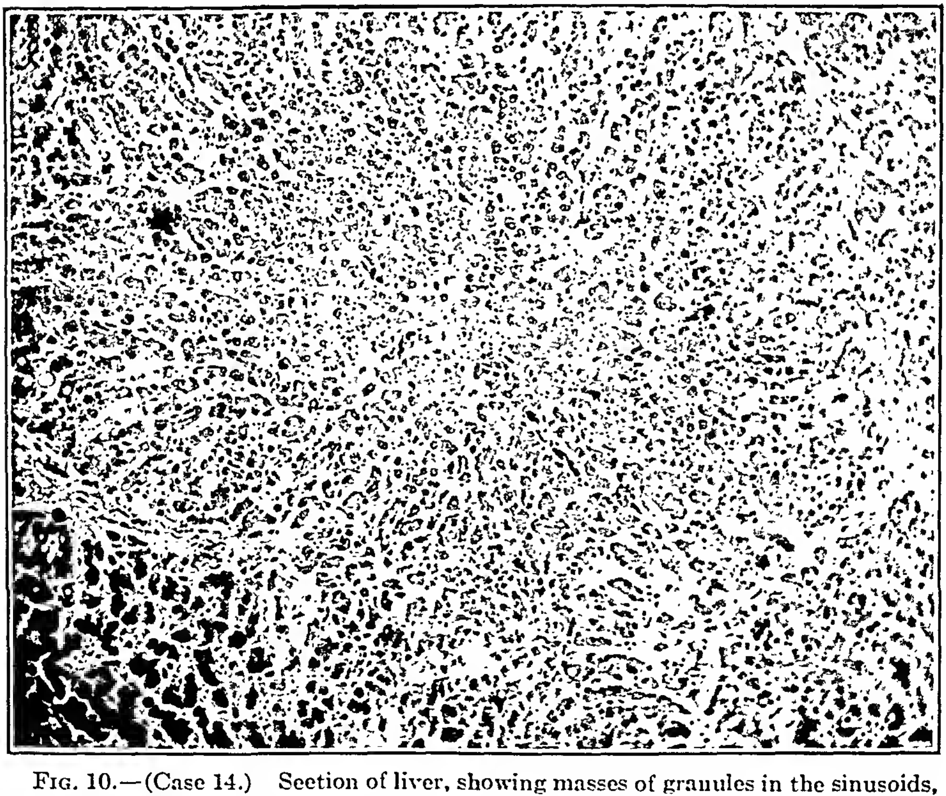

Fig. 10.—(Case 14.) Section of liver, showing masses of granules in the sinusoids, with some evidence of accumulation about the central veins, at least toward the central zone, and little in the portal areas.

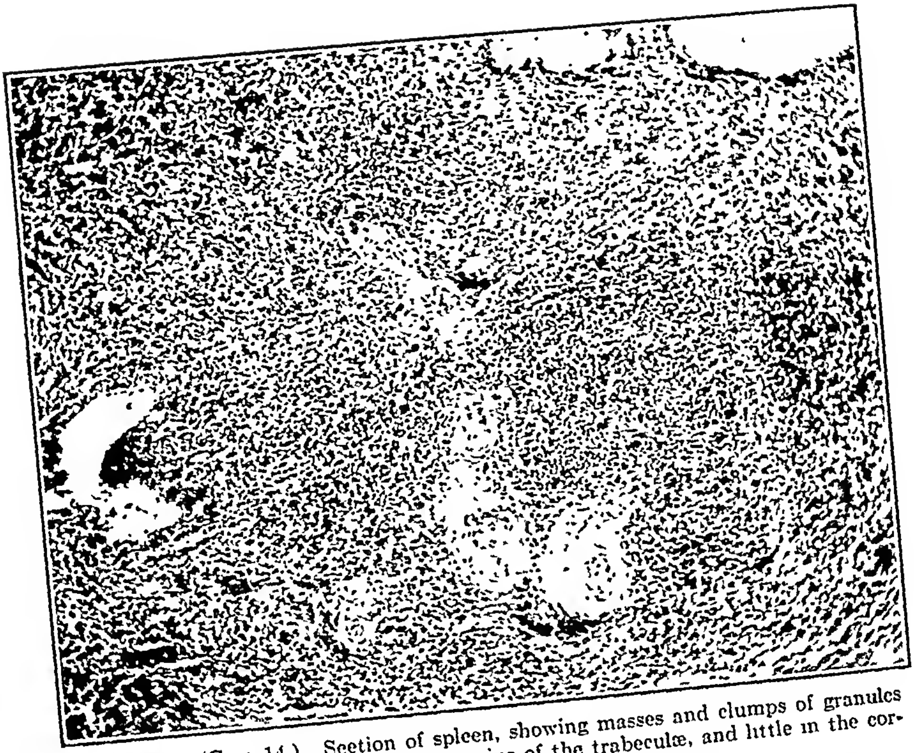

Fig. 11.—(Case 14.) Section of spleen, showing masses and clumps of granules throughout the pulp and along the margins of the trabeculæ, and little in the corpuscles, except about the central vessels.

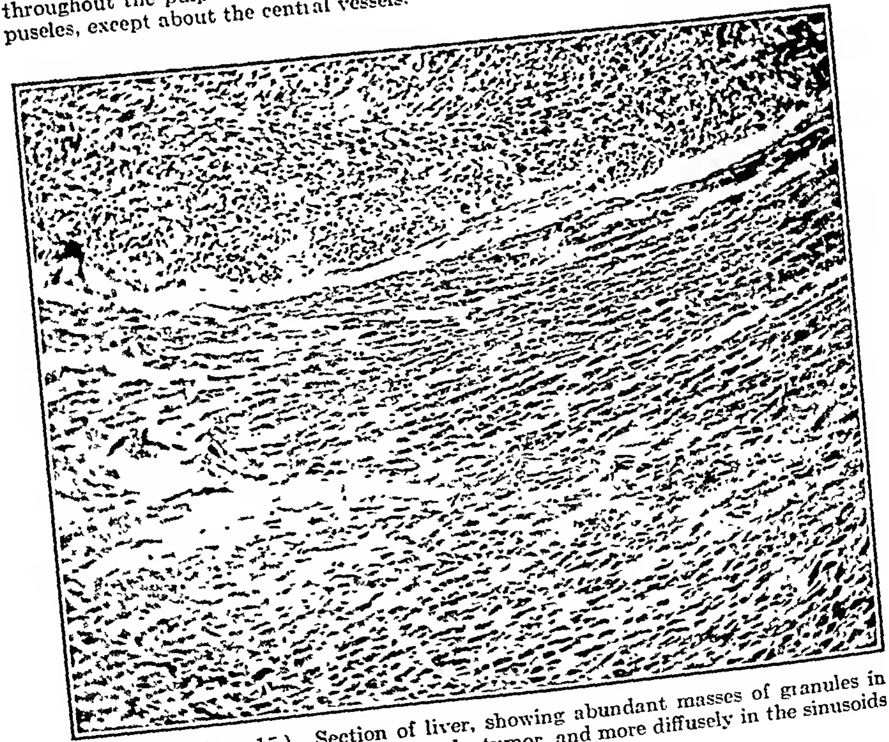

Fig. 12.—(Case 15.) Section of liver, showing abundant masses of granules in strands in the connective tissue about the tumor, and more diffusely in the sinusoids of the rest of the liver.

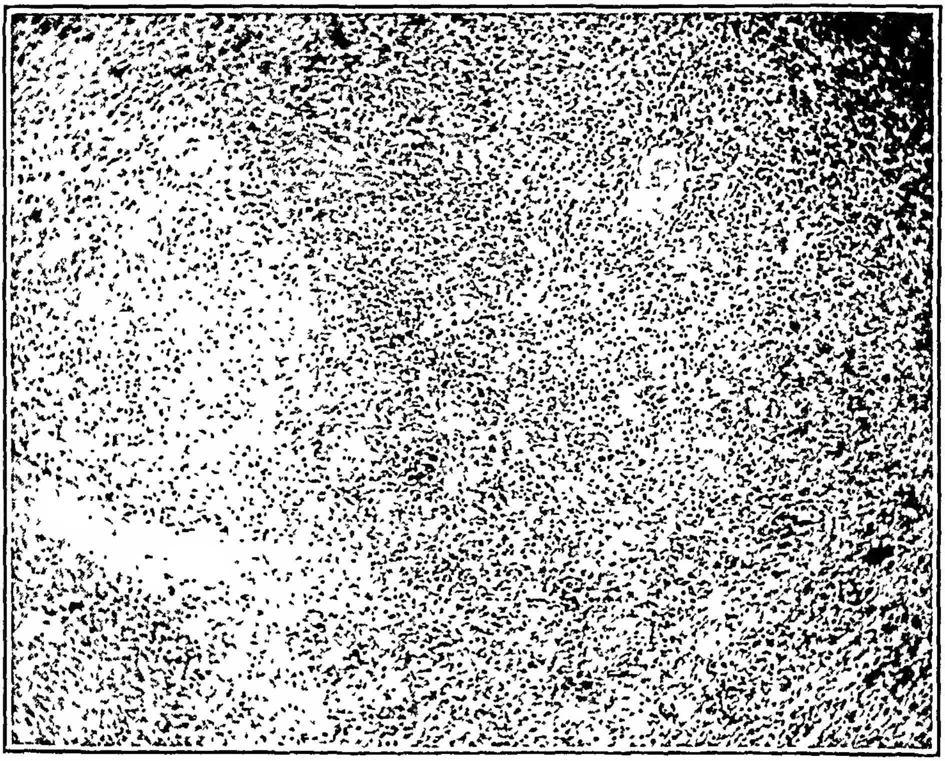

FIG. 13.—(Case 15.) Section of spleen, showing abundant masses of granules in clumps and blotches through the pulp, less in the corpuscles, and no special concentration about the trabeculæ.

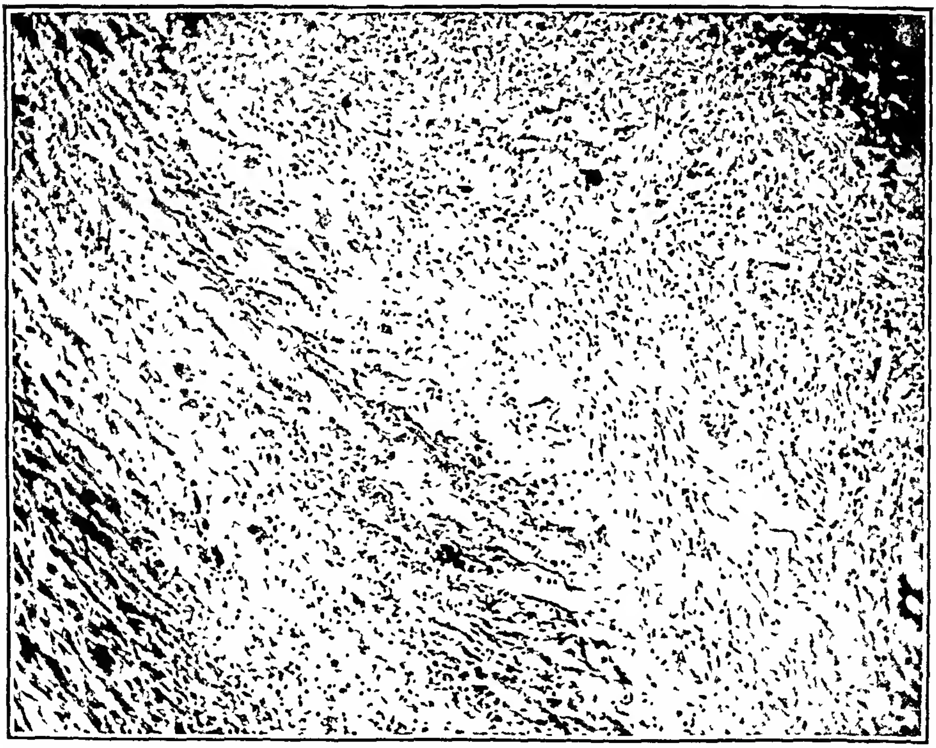

FIG. 14.—(Case 16.) Section of liver, showing clumps of granules in the sinusoids, diffusely throughout the lobules.

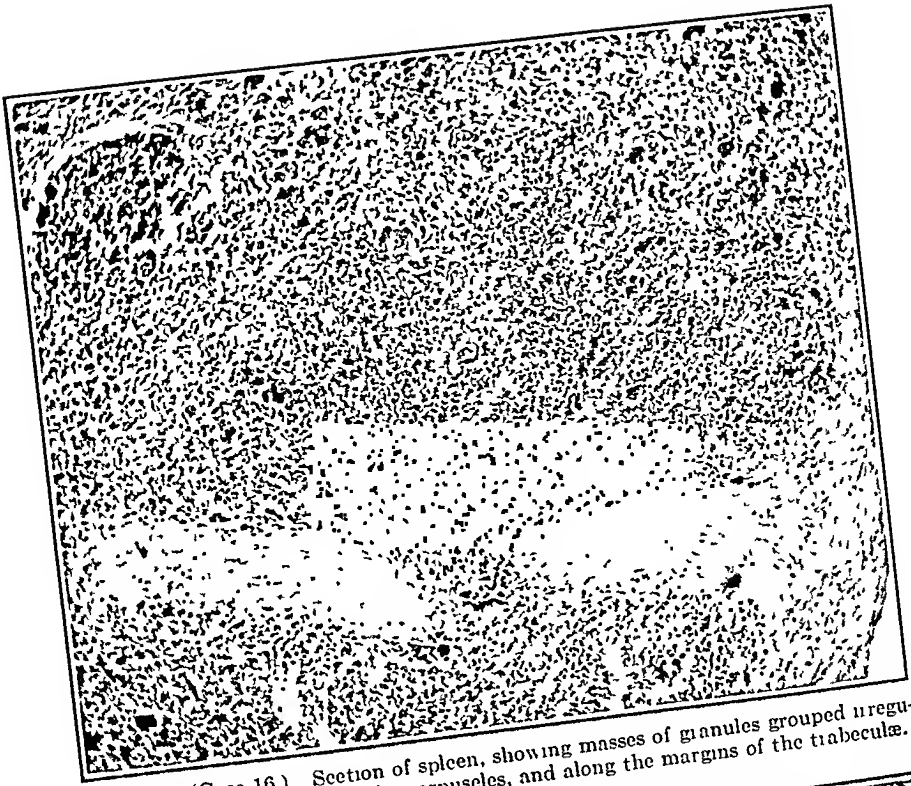

FIG 15.—(Case 16.) Section of spleen, showing masses of granules grouped irregularly through the pulp, in the corpuscles, and along the margins of the trabeculæ.

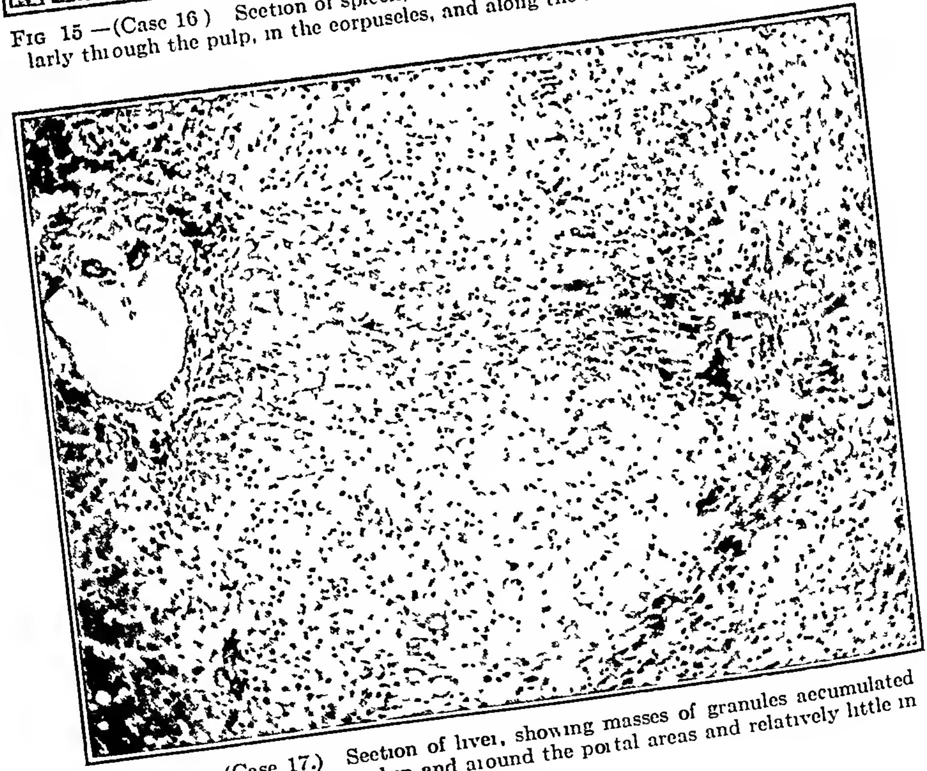

FIG 16.—(Case 17.) Section of liver, showing masses of granules accumulated around the central veins and in and around the portal areas and relatively little in the sinusoids throughout the liver.

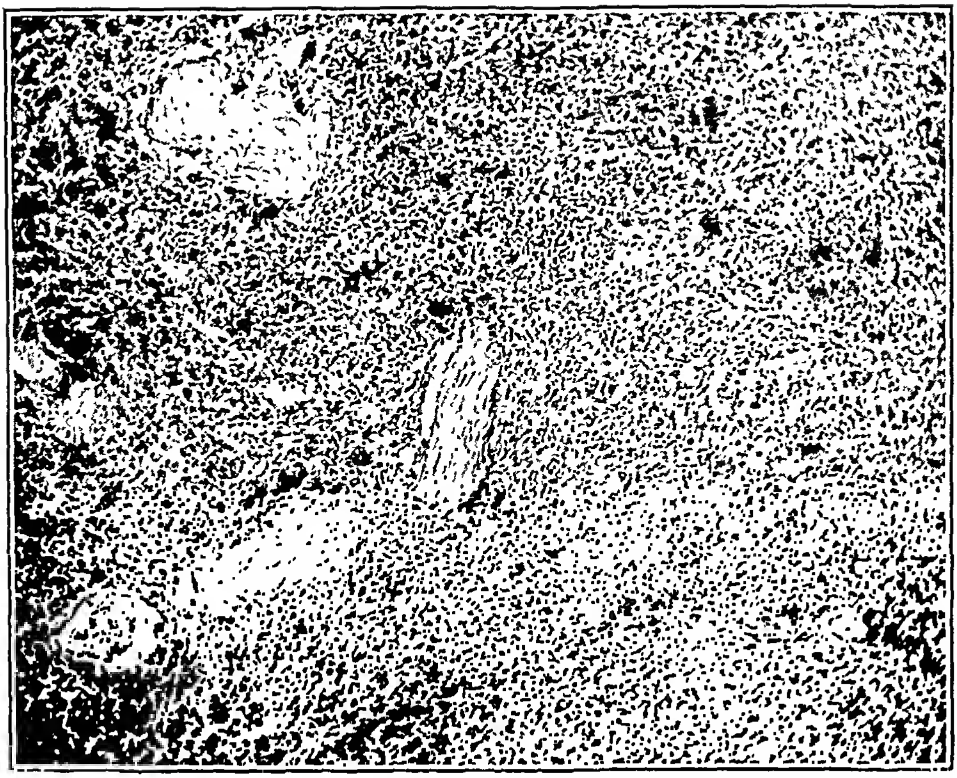

Fig. 17.—(Case 17.) Section of spleen, showing abundant masses of granules in clumps and strands in the pulp, some about the central vessels in the corpuscles and no accumulation about the trabeculæ.

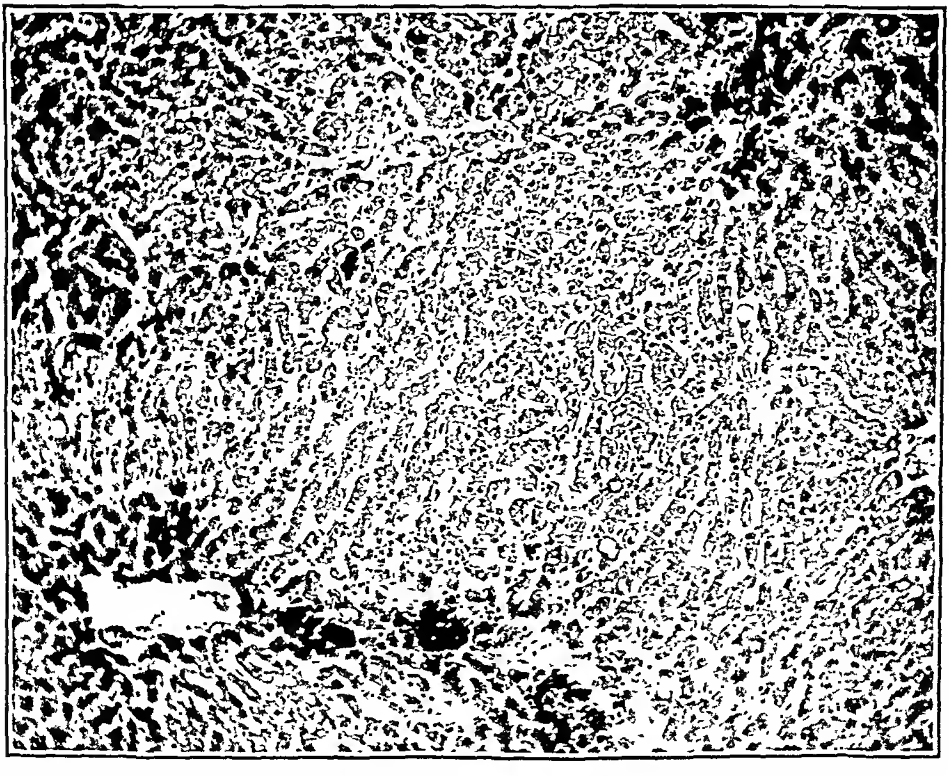

Fig. 18.—(Case 18.) Section of liver, showing large masses of granules, especially about the central veins and about the portal areas.

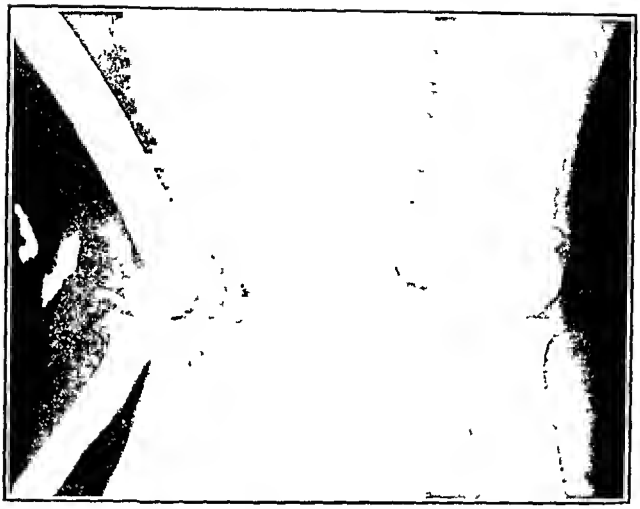

Fig. 19.—(Case 5.) Two areas of radio-opacity at the site of the injections of Thorotrast.

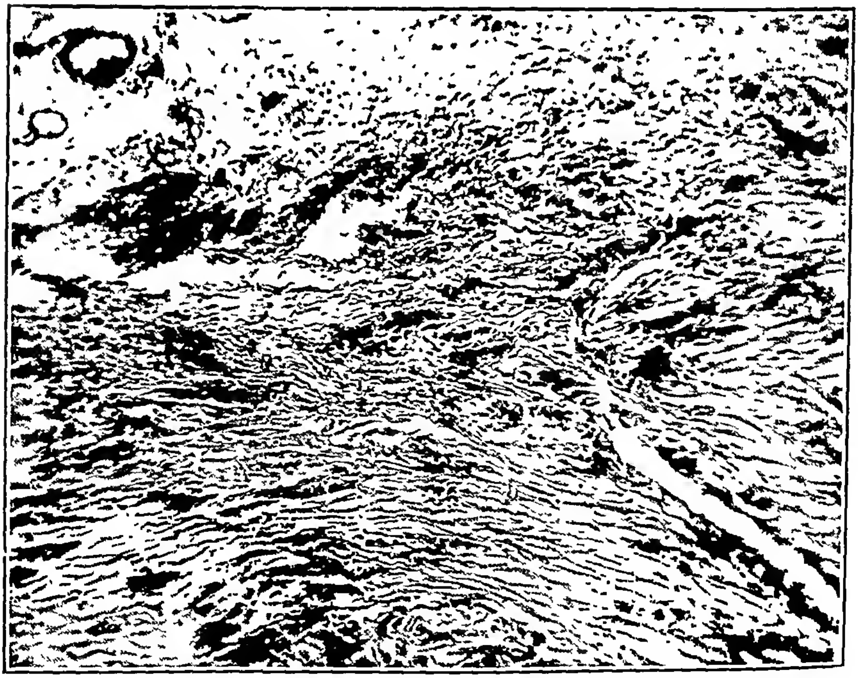

Fig. 20.—(Case 5.) Section of the nodule, showing strands of dense hyaline connective tissue, separated by abundant masses, clumps, and strands of grayish-brown granules. Nowhere is there any evidence of recent cellular reaction through the fibrous tissue, about the masses of granules, or about the blood-vessels.

the basis of time since the injection and the condition for diagnosis of which the injection was made. Since time after the injection is the more important factor, the cases have been arranged according to the time following the injection.

A. **Liver and Spleen.** Of 64 cases coming to necropsy and studied histologically, the following 8 cases have been chosen as illustrative of the behavior of thorium dioxide and the reaction of the tissues after various lengths of time following the injection and in various conditions.

Case 11.—J. B., a 55-year-old colored man, was given Thorotrast 5 days before necropsy. Necropsy diagnosis: carcinoma of the stomach, with metastases to the liver, pancreas, regional lymph nodes, urinary bladder and left adrenal. Microscopically, the liver section shows masses of granules in the sinusoids, with no concentration about the central veins or in the portal areas. The spleen section shows masses of granules distributed through the pulp; there is none in the Malpighian corpuscles, and no special accumulation about the trabeculæ (Figs. 4 and 5).

Case 12.—C. P., a 50-year-old colored man, was given Thorotrast 9 days before necropsy. Necropsy diagnosis: primary carcinoma of the duodenum. Microscopically, the liver section shows masses of granules in the sinusoids, with no accumulation about the central veins or in the portal areas. The spleen section shows granules scattered diffusely throughout the pulp, with few masses and no clumps of granules; there is less of the granular material in the corpuscles, and no accumulation of the granules about the trabeculæ (Figs. 6 and 7).

Case 13.—J. H., a 56-year-old white woman, was given Thorotrast 1 month before necropsy. Necropsy diagnosis: cirrhosis of the liver. Microscopically, the liver section shows areas of liver cells surrounded by bands of fibrous tissue; the liver structure is gone. There are masses of granules in the sinusoids between the liver cells. The spleen section shows abundant masses of granules throughout the pulp; very little in the corpuscles and no accumulation about the trabeculæ (Figs. 8 and 9).

Case 14.—L. H., a 45-year-old colored woman, had a panhysterectomy on the clinical diagnosis of carcinoma of the uterus, but no cancer found in the organs removed. Necropsy was performed 5 months after injection of Thorotrast. Necropsy diagnosis: healed gastric ulcer; healed adhesive peritonitis; bronchopneumonia. Microscopically, the liver section shows masses of granules in the sinusoids with some evidence of accumulation about the central veins, at least, toward the central zone; there was little in the portal areas. The spleen section shows masses and clumps of granules throughout the pulp and along the margins of the trabeculæ, but little in the corpuscles, except about the central vessels (Figs. 10 and 11).

Case 15.—C. J., a 23-year-old colored woman, had an amputation of the thigh for sarcoma of the knee. Necropsy was performed 6 months after injection of Thorotrast. Necropsy diagnosis: metastatic sarcoma in the lungs, liver and myocardium. Microscopically, the liver section shows abundant masses of granules in strands in the connective tissue about the tumor and more diffusely in the sinusoids of the rest of the liver. The spleen section shows abundant masses of granules, in clumps and blotches, throughout the pulp, with less in the corpuscles; there is no special concentration about the trabeculæ (Figs. 12 and 13).

Case 16.—L. C., a 50-year-old colored woman, was given Thorotrast one year before necropsy. Necropsy diagnosis: carcinoma of the stomach; obstruction of the bile ducts; multiple abscesses in the liver. Microscopically, the liver section shows clumps of granules in the sinusoids, diffusely throughout the lobules. The spleen section shows masses of granules grouped irregularly through the pulp, in the corpuscles, and along the margins of the trabeculæ (Figs. 14 and 15).

CASE 17.—A. F., a 47-year-old white man, was given Thorotrast 15 months before necropsy. Necropsy diagnosis: multiple lymphoma, generalized; bronchopneumonia; lung abscesses, right. Microscopically, the liver section shows masses of granules accumulated around the central veins and in and about the portal areas; there is relatively little in the sinusoids throughout the liver. The spleen section shows abundant masses of granules in clumps and strands in the pulp, some about the central vessels in the corpuscles, and no accumulation about the trabeculæ (Figs. 16 and 17).

CASE 18.—L. A., a 44-year-old white man, was given Thorotrast 3 years before necropsy. Necropsy diagnosis: malignant melanoma, with metastases to the brain; no metastases in the liver. The patient died soon after entering the hospital, and the coroner made the necropsy. Microscopically, the liver section shows large masses of granules, especially about the central veins and about the portal areas. The spleen was not saved (Fig. 18).

In all cases, the picture is very much the same, with the granules scattered diffusely in the liver in the earlier months after injection, and some tendency to accumulate about the central veins and in the portal areas in the later months after injection. There is little indication of any shifting in the spleen from the early to the later months.

In none of the cases is there any evidence of injury to the cells in the immediate neighborhood of the granules of thorium dioxide, or anywhere in the liver or spleen, that can be ascribed to the thorium dioxide. Neither is there any cellular reaction in the neighborhood of the granules, or anywhere in the liver and spleen, that can be ascribed to the thorium dioxide.

B. **Subcutaneous Nodule.** In view of the reports of injurious effects from the injection of Thorotrast into the tissues of lower animals, it is important to know the reaction when the substance is injected into the tissues of the human. We have had the opportunity to study a subcutaneous nodule, resulting from leakage of some of the Thorotrast about the site of injection into the vein.

CASE 5.—L. B., a 13-year-old white girl, was injected with 8 cc. of Thorotrast on December 1, 1932, to rule out rupture of the spleen, the result of an accident. The spleen was found to be normal; the patient recovered without operation. There was some leakage around the site of the injection; a firm nodule developed at that area; and we have been able to study this nodule 4 years and 5 months after the injection. Microscopically, the section of the nodule shows strands of dense hyaline connective tissue, separated by abundant masses, clumps and strands of grayish-brown granules. Nowhere is there any evidence of recent cellular reaction through the fibrous tissue, about the masses of granules, or about the blood-vessels (Figs. 19 and 20).

In this case, the patient was 8½ years of age at the time of injection. While there is an abundance of thorium dioxide remaining in the nodule, there is no evidence of any cellular reaction, other than the primary reaction walling off the material. The microscopic picture reminds one of the nodules seen in the nodular form of silicosis, except that in this case the granules of thorium dioxide are seen in abundance.

Summary of Histopathologic Study. 1. Necropsies have been performed on 64 patients at intervals of a few days to 3 years after the injection of an average dosage of 75 cc. of Thorotrast for the purpose of making hepatosplenograms. In no case was there any evidence of injury to the tissues nor cellular reaction that could be ascribed to the presence of the thorium dioxide.

2. A subcutaneous nodule was excised from the arm 4 years and 5 months after the injection of Thorotrast accidentally into the subcutaneous tissues. The thorium dioxide was walled off by dense hyaline connective tissue, the nodule resembling those found in the lungs in nodular silicosis. Nowhere was there any evidence of injury to the tissues nor cellular reaction other than the primary reaction resulting in the walling-off of the thorium dioxide.

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AN EVALUATION OF THE CONGO-RED TEST FOR AMYLOIDOSIS.

A CORRELATION OF THE AUTOPSY FINDINGS AND DYE ABSORPTION IN 125 CASES.

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BENNHOLD[1] in 1923 reported that an aqueous solution of Congo-red, injected intravenously, disappeared from the blood stream more rapidly in the presence of amyloidosis than in its absence. Upon this basis Congo-red has been used with increasing frequency as a laboratory aid to confirm a clinical diagnosis of amyloidosis.

In 1915, Keith, Rowntree and Geraghty,[5] working with Congo-red in the determination of blood volume, found that upon injection into the blood stream, it became homogeneously distributed in the plasma in 4 minutes, began to disappear in 10 minutes, and in the normal, all the dye had left the blood at the end of 24 hours. Bennhold, by studying the behavior of the dye in normal and various pathological conditions, concluded that 11 to 30% of the dye would usually disappear at the end of 1 hour and that the disappearance of 60% or more indicated the presence of amyloid disease. The rapid disappearance of the dye, according to Bennhold, was due to the absorption of the dye by amyloid substance. The dye was filtered out more rapidly from the blood because of the damaged capillary endothelium which he postulated was present in such cases.

Furthermore, he stated that any failure of the typical disappearance of the dye was evidence only against widespread amyloidosis, and especially against amyloidosis of the liver. Deposits in the kidney alone did not have sufficient volume to give the typical reaction. Confirmation of these clinical and laboratory findings was attempted in 9 cases which came to autopsy. In 6 cases in which the dye had speedily disappeared from the blood, amyloid degeneration was demonstrated.

Schoenberger and Rosenblatt,[8] in 1925, corroborated Bennhold's results in a small number of cases, concluding that 41% or more of the dye will disappear in the presence of amyloidosis at the end of 1 hour against 11 to 29% in normal subjects. No mention was made of autopsy confirmation. Reports by Bookman and Rosenthal,[2] Wallace,[13] and Shapiro[9] also confirmed Bennhold's observations.

At the present time a figure of 50% or better is commonly accepted in the literature as proof of the presence of amyloidosis. Rosenblatt,[6] in an extensive review of the literature concerning the clinical aspects of amyloidosis in 1934, states: "A positive diagnosis of amyloidosis should not be made unless over 50% of the dye has been retained by the tissues in 1 hour. Because of this ability to make a definite premortem diagnosis there has been established a greater appreciation of amyloid disease as a clinical syndrome." Boyd[3] states that the clinical diagnosis of amyloid disease can be confirmed by the Congo-red test if 60% or more of the dye has disappeared at the end of 1 hour from the blood.

In an institution such as this hospital, in which the great majority of patients have advanced pulmonary disease with its attendant complications, amyloidosis is encountered with relative frequency, and the Congo-red test has been used extensively to confirm or exclude the clinical diagnosis of the disease. In the past, however, in certain instances in which a clinical diagnosis had been made of amyloidosis and confirmed by Congo-red absorptions of 60 to 75%, autopsy findings failed to corroborate the clinical diagnosis. In this present series 2 such cases were also observed. Therefore it was determined to run a large series of cases in which the Congo-red test was to be given not only to those cases in which amyloidosis was clinically suspected, but to any critically ill patient in which the test was possible. Through this procedure it would then be possible to correlate more definitely the percentage of Congo-red absorption with the presence or absence of amyloid changes in the various organs when such cases came to autopsy. Also by analyzing such factors as the pathologic findings, Congo-red percentage of absorption and the distribution of amyloidosis, it might be possible to determine the presence of any constant factors which would be of aid in explaining the results obtained.

The technique of the test as introduced by Bennhold has been only slightly modified up to the present time. He introduced 10 cc. of a 1% aqueous solution intravenously and then collected 10 cc. of blood at the end of 4 minutes and 1 hour. The colored serum of the 4-minute specimen was used as the standard against which the serum of the 1-hour specimen was compared using any standard colorimeter. No hemoglobin-precipitating agent was used, as reliance was placed upon the use of paraffin tubes and careful centrifuging to obtain sera free from hemoglobin coloring matter. Since the presence of even a very small amount of hemoglobin in the serum will interfere seriously with the test, the Bennhold technique has been modified at this laboratory. Friedman and Auerbach[4] used alcohol as a protein-precipitating agent, obtaining a clear colored solution of Congo-red in alcohol. However, the quantity of alcohol necessary made too great dilutions of the dye, and Taran[11] in a series of experiments found that acetone can be used just as effectively in much smaller amounts. With the use of acetone one gets clear solutions of the dye with varying intensities of color, depending upon the amount of dye present. In a small percentage of cases, however, the test is not satisfactory as practically all of the dye apparently leaves the blood stream in a few minutes with the result that the 4-minute standard specimen as well as the hour specimen contain very little or no dye. Three such cases have come to autopsy. Errors in the technical or laboratory technique were ruled out as the tests were repeated under carefully controlled conditions. In each instance, upon repetition of the test, similar results were obtained. In 2 of these cases the liver and spleen were greatly enlarged and contained large deposits of amyloid substance. In these cases the possibility exists that enough amyloid was present to absorb most of the dye in the 4-minute interval. The third case had no amyloidosis. Bennhold and Takeda[10] have demonstrated by means of biliary drainage, biliary fistulæ and ligation of the main biliary ducts that almost all of the Congo-red dye is excreted by the liver into the bile and that the reticulo-endothelium system plays little or no part in its disappearance. In such cases, therefore, where the dye disappears with extreme rapidity in the absence of amyloid changes, it may be due to an increased excretory action by the liver.

This study consists of an analysis of 125 autopsies which were performed on cases in which a Congo-red test had been done. Amyloidosis was diagnosed in the usual manner, that is the use of iodine grossly and Congo-red or methyl violet staining for microscopic sections. In all of these cases tuberculosis with its attendant complications was the predominant picture and the patients ranged in age from 2 to 72 years.

At autopsy, amyloidosis was present in 34 of these cases and absent in 91. The correlation of the percentage of Congo-red absorption in these cases is demonstrated in Figure 1.

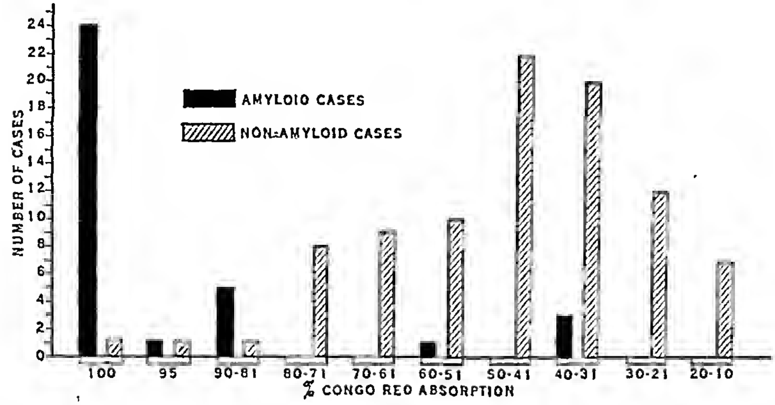

FIG. 1.—Analysis of the percentage of Congo-red absorption in the presence and absence of amyloidosis at autopsy.

In the presence of amyloid changes there is almost complete absorption of the dye within 1 hour in the great majority of cases. In 29 of the 34 amyloidosis cases the percentage of absorption was 90% or higher, with complete absorption of the dye in 24 of these cases. There were 5 cases recorded in the amyloid group with absorptions of the dye below 90%. These were as follows: 82%, 60%, and 3 cases with 35% absorptions. Postmortem examination in 4 of these cases revealed minimal or moderate amyloid changes and the spleen was the only parenchymatous organ involved grossly. The liver in all of these cases was free of amyloid deposits. A possible explanation for the low absorption values in these instances is that there were not sufficient amyloid deposits to absorb the dye. The other case had a 35% absorption despite extensive amyloid deposits in the spleen, kidneys and liver. The test, however, was performed 6 months before the patient expired and in this case there is the distinct possibility that the test had been performed before sufficient amyloid disease was present to give a high percentage of absorption.

In the 91 cases in which no amyloidosis was present the percentage of Congo-red absorption in 87 of the cases varied from 10 to 75% with the greatest incidence in the 41 to 50% group and the greatest proportion of cases (61) ranging in percentage values of 50% or below. In the remaining 4 cases there were percentage values of 100, 95, 90 and 80%, despite no evidence of amyloid at autopsy. Unfortunately none of these cases had more than one test performed. One must always consider the possibility of error in the technique of the test, as for example, the use of the same syringe which contained the dye to withdraw the 4-minute specimen. The small amount of dye remaining in the syringe is sufficient to add much color to the serum and accordingly give false readings which in such cases are too high. Also in some cases all of the dye is not injected into the blood stream and this may give false readings.

Although amyloid degeneration has been reported in almost every organ in the body, it is by far most commonly present in the spleen, liver, kidneys and adrenals in the order named, and it is the involvement of these organs which gives the syndrome of generalized amyloidosis. In the 34 cases of this series, amyloid was distributed as follows (Table 1).

TABLE 1.—DISTRIBUTION OF AMYLOID SUBSTANCE.

Organs involved.	Number of cases.
Spleen	32
Kidney	28
Liver	25
Adrenal	23
Lymph nodes	9
Blood-vessels	3
Pancreas	2
Intestinal tract	2

In 28 of the 34 cases, the kidneys, spleen, liver and adrenals were simultaneously involved. The remaining cases demonstrated singular involvement of the spleen and kidneys, and involvement of the liver and spleen or kidneys and spleen. Along with involvement of these four organs, microscopic examination also revealed small areas occasionally in the pancreas, lymph nodes, intestinal tract and the walls of the smaller blood-vessels. Although Bennhold's statement is generally true that one cannot expect the typical rapid disappearance of the dye unless there are widespread amyloid changes with involvement especially of the liver, exceptions are to be found. In 1 case, in which gross and microscopic examination revealed deposits only in the kidney (with the exception of a few areas in the arterioles of the spleen) there was complete absorption of the dye. In the other instance there were deposits in the spleen and kidneys, but no deposits in the liver and again there was a 100% absorption. It therefore appears likely that any of the larger parenchymatous organs can have sufficient amyloid deposits to give complete or almost complete absorption of the dye, although it is very uncommon to find unique involvement of these organs. This was also confirmed by Rosenblatt[7] who found in one of his cases a 95% absorption with only the kidneys and adrenals involved.

To facilitate the correlation of the lesions in those cases where amyloidosis was present with those in which no amyloidosis was demonstrable, an arbitrary division into seven groups was made (Table 2).

From Table 2 it can be readily determined that the type and distribution of the lesions are very similar in both the amyloid and non-amyloid cases. Caseous pneumonic tuberculosis (uncomplicated by bone or other suppurative foci) was the most frequent finding, but the other groups are represented in both the amyloid and non-

TABLE 2.—CORRELATION OF THE PATHOLOGICAL CHANGES WITH THE PRESENCE OR ABSENCE OF AMYLOIDOSIS.

Lesions.	Number of amyloid cases.	Number of non-amyloid cases.
1. Caseous pneumonic tuberculosis (uncomplicated by bone or suppurative foci)	19	64
2. Caseous pneumonic tuberculosis with empyema	8	11
3. Caseous pneumonic tuberculosis with osteomyelitis	3	6
4. Caseous pneumonic tuberculosis with empyema and osteomyelitis	1	4
5. Hematogenous pulmonary tuberculosis and osteomyelitis	2	3
6. Hematogenous pulmonary tuberculosis and genito-urinary tuberculosis	0	3
7. Osteomyelitis, with no pulmonary lesions	1	0

amyloid groups, with the exception of a case of tuberculous osteomyelitis of the orbit in a child with a calcified primary focus, and 3 cases of hematogenous pulmonary tuberculosis associated with tuberculosis of the genito-urinary tract.

As for the duration of these pathologic processes, it is difficult to get accurate estimates. In both groups the terminal hospitalization ranged from 1 month to 12 years with the average period between 1 and 2 years. One must not lose sight of the fact that all of these patients, with very few exceptions, entered the institution with a far-advanced spread of the disease and died as a result of the pulmonary tuberculosis or its attendant complications. Since it is commonly agreed that sufficient amyloid changes will usually develop from 1 to 2 years after the onset of a suppurative or destructive lesion (Walker,[12] Whitbeck[14]) to give clinical evidence of its existence, there is no question that in this series this factor, *i. e.*, the duration of the disease, offers no aid in explaining the presence of amyloid in the one group and the absence of amyloidosis in the other. Similar pathologic findings were represented and the duration and severity of these processes were also closely approximated in both groups.

A comparison of the age incidence in both groups also revealed a parallel similarity. The non-amyloidosis group ranged from 2 to 72 years and in the amyloidosis group the youngest was 3 and the oldest 52.

Finally, this study confirms the observation that although amyloid changes are infrequent findings at the autopsy table even in large general hospitals, the incidence rises sharply in tuberculosis institutions. Rosenblatt,[7] in a series of 1727 autopsies, found the incidence to be 7.2%. But in those cases suffering from tuberculosis, the incidence rose to 24.4% and the incidence in the non-tuberculous fell to 1.2%. From that study and other observations he concluded that tuberculosis is by far the greatest single etiologic factor in the production of amyloidosis and this has been confirmed by other investigators. In this series amyloidosis was present in 27.2% of the cases. In a statistical survey of approximately 1000 autopsies at this hospital, the incidence was found to be 20%.

Summary and Conclusions. 1. An attempted evaluation of the Congo-red test for amyloidosis was studied by the correlation of the percentage of absorption of the dye with the presence or absence of amyloidosis in a series of 125 autopsies upon tuberculous patients ranging in age from 2 to 72 years.

2. Amyloidosis was present in 34 of the 125 cases, an incidence of 27.2%.

3. In the presence of amyloidosis, the percentage of Congo-red absorption ranged between 90 to 100% with 70% of these cases having complete absorption of the dye. Exceptions were present in 5 instances, with absorption values of 82, 60 and 3 cases of 35%.

4. In the absence of amyloidosis, the percentage of dye absorption ranged between 10 and 75% in all instances with the exception of 4 cases in which values of 80, 90, 95 and 100% were recorded.

5. The Congo-red test can be interpreted only as confirmatory evidence of amyloid disease when the percentage of dye absorption is 90% or higher.

6. The organs which had amyloid involvement most frequently were the spleen, kidneys, liver and adrenals in the order named. The presence of amyloidosis in the kidneys alone can result in a 100% absorption.

7. A comparison of the type and duration of the disease present failed to reveal any factors which might account for the presence of amyloidosis in 34 cases and its absence in the remaining 91 cases.

I wish to thank Dr. Oscar Auerbach, Director of Laboratories, for his aid and interest in the preparation and completion of this work.

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THE BLOOD PRESSURE AND PULSE RATE AS AN INDEX OF EMOTIONAL STABILITY.

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In a previous communication[2] dealing with the interpretation of blood pressures and pulse rates in routine physical examinations, it was pointed out that the most frequent and serious source of error was caused by the reaction of the cardiovascular system to the emotional stress of the examination itself. It was further stated that the quantative reaction of the cardiovascular system depended on the relative stability of the individual being examined and it was suggested that there was probably a high degree of correlation between the two.

If such a correlation could be established, then the reaction of the cardiovascular system to a routine physical examination or to any other suitable emotional stimulus could be utilized as an index of emotional stability. Such a simple objective test would not only add a valuable new diagnostic tool to the armament of the general medical profession but would also be a welcome substitute for the present time-consuming, subjective, analytical procedure now in use by psychologists. Furthermore, such a test would be a boon to insurance companies, industrial concerns, Government Bureaus and Departments and all other agencies who are desirous of gaining a better psychologic picture of the great numbers of individuals with whom they are concerned without resorting to undue time-consuming and expensive clinical investigations.

There have been a great many past attempts to establish a correlation between cardiovascular reactions and psychic stimuli, but to date these have not been attended with any high degree of success. Many significant facts bearing on this question have been fairly well established, however, and these may be briefly stated as follows: Marston[10] and Scott[15] found that any psychic stimulus which produces an emotional reaction produces a change in the systolic blood pressure, usually a rise, but they disagree as to whether or not there is a correlation between the degree of emotion and the cardiovascular change. In a review of the examinations for the Royal Air Force, Threadgold[17] showed that there was a marked rise in the average systolic blood pressures during original examinations which tended to disappear on subsequent reëxaminations. Schneider,[13] discussing the altitude classification test for aviators, stated that individuals with high systolic pressures reacted more to a given psychic stimulus by higher systolic rises and higher pulse rates or both, than those with low systolic pressures. That the blood pressure and pulse is lowest during sleep, while the mind is entirely free from emotional stimuli, was determined by Boas and Goldschmidt[3] and this was supported by the work of MacWilliams[9] who further showed that dreams produced a marked rise. Other authors, who have presented studies which support the general conclusions stated above, are notably Stevens[16] studying psychoanalysis, Schultz[14] studying autosuggestion, Adler and Larson[1] studying deception, Gillespie[6a] and Landis and Gullette[8] studying various emotional stimuli, and Deutsch and Kauf[5] studying psychic trauma in relation to cardiovascular reactions.

Thus while it seems well established that the cardiovascular system does react to psychic stimuli; that the reaction is usually a rise in the systolic blood pressure or of the pulse, or both; and that these rises are not constant for a given stimulus, it should be noted that the literature in this field contains no study of the reaction of the cardiovascular system as a whole in relation to the relative stability of the individual.

Present Study. The present study was undertaken with the object of determining the reaction of the cardiovascular system as a whole to a given emotional stimulus and to determine the correlation between this reaction of the cardiovascular system and the relative emotional stability (within the range of normal) of the individual. The data for this study were derived from original examination forms of 700 applicants for flying training of the United States Army Air Corps. Of these 700 examinations, 212 were those of the author while the remaining 488 were secured from official files and represent the work of others divided as follows: Examiner A—106 forms; Examiner B—84 forms and Examiners C (a miscellaneous group)—298 forms. The forms in each instance were taken consecutively except where candidates were shown to be suffering from a neurosis, a psychosis or any organic cardiovascular disease.

The candidates were all young male adults between the ages of 18 and 28 years with two or more years of college education and in general were high type individuals. The examinations were conducted in accordance with Army Regulation 40–110 which specifically outlines the procedures to be followed. The blood pressures and the pulse rates used were those secured at the first reading after the candidate had been reclining quietly for 5 minutes.

The relative emotional stability of each individual was determined by a personality study by which he was classified as being "stable" or "unstable." A stable individual in this examination is one who, in the opinion of the examiner, shows a hereditary background of no insanity or other nervous diseases in ancestors or collateral branches of the family; who himself exhibits traits of normal inhibition, emotional control and rational balance; and who by his past history of dealing with situations has demonstrated a durable nervous and mental mechanism capable of withstanding the acute shock of flying training and the chronic stress of a lifetime of flying.

The emotional stimulus in this study was the examination itself. That a general physical examination is an emotional stimulus is too widely accepted to need further comment but this fact may be further emphasized by pointing out that, at least in the type of examination considered in this study, the individual during the examination is subjected to: 1, A strange environment (uncertainty, apprehension); 2, A strange examiner (timidity, shyness); 3, Bodily exposure (resentment, embarrassment); 4, A desire to pass (anxiety, fear); 5, Compression of brachial artery (discomfort, tingling sensation).

Thus the examination is not a stimulus to any one emotion but to the total emotional content and the resultant reaction should be a measure of the reaction of the individual as a whole.

Findings. Of the 700 candidates examined 399 (57%) were considered unstable and 301 (43%) stable as determined by the personality study. By the trial and error method it was then determined that the best correlation between emotional stability and the cardiovascular findings was obtained when a systolic blood pressure above 134, a diastolic blood pressure above 90 or a pulse rate above 90, or any combination of these, was considered as indicating instability. Realizing that such an arbitrary figure in a constantly fluctuating medium was too narrow for practical purposes, a blood pressure-pulse range of the above figures, + or −3, was adopted and all findings within that range were considered borderline cases and credited with agreeing with the results of the personality study.

The correlation between the emotional stability and the cardiovascular reaction, as determined by the above method, is shown in Table 1. The 212 forms of the author's were further studied as to the distribution of the various blood pressure-pulse patterns (Table 2).

TABLE 1.—CORRELATION BETWEEN RELATIVE EMOTIONAL STABILITY, AS DETERMINED BY A PERSONALITY STUDY, AND REACTION OF THE CARDIOVASCULAR SYSTEM TO A GIVEN EMOTIONAL STIMULUS.

	Number of candidates.	Correlation.		
		Stable.	Unstable.	Average.
Author	212	.99	.95	.965
Examiner A	106	100	.98	.996
Examiner B	84	.98	.93	.95
Examiners C	298	.97	.79	.85
Total	700	.98	.88	.92

Discussion. Aviation medicine is a specialty composed of several specialties. It is therefore not to be expected that all students of aviation medicine are able to master all phases of the subject as thoroughly as if it were composed of one specialty. From this standpoint alone it is believed that the correlation (Table 1) is minimal and probably lower than that which actually exists. This statement is based on the following facts: Examiner A, who had the highest correlation, is especially interested in psychology and has had an excellent training and experience in that field. The author and Examiner B, who had a somewhat lower correlation in their cases, have never exhibited any disproportionate interest in this phase of aviation medicine and are probably qualified in psychology only in proportion to our limited experience. Personally, I would hesitate to say that, for the amount of time available for the large number of examinations given, I was infallible in the estimation of every candidate's emotional stability. Especially is this true when it is remembered that most of these candidates have col-

TABLE 2.—THE BLOOD PRESSURE-PULSE PATTERNS AND THEIR DISTRIBUTION IN 212 STABLE AND UNSTABLE CANDIDATES.

Type.	Subtype.	No. cases.	% of total cases.	Average blood pressure.	Average pulse.
Stable	Normal	101	47.64	119–70	80
	Athletic	12	5.66	103–60	74
Unstables.	High systolic Normal diastolic Normal pulse	59	27.9	140–79	81
	High systolic High diastolic Normal pulse	7	3.3	142–96	80
	High systolic High diastolic High pulse	6	2.8	141–96	96
	High systolic Normal diastolic High pulse	6	2.8	148–75	102
	Low systolic Low diastolic High pulse (fainters)	21	9.9	102–58	97

lege degrees and that many have had college courses in psychology and are not averse to utilizing their knowledge in the "battle of wits" to give answers which are most favorable and not necessarily the most truthful concerning their antecedents and their own past behavior.

Examiners C, who as a group had the lowest correlation, exhibit evidence of certain defects and omissions in the psychologic examination. For example, many of their candidates were not classified as being either stable or unstable (these cases were omitted from this study) showing a lack of interest in, or an appreciation of, that phase of the examination. Furthermore, the decision reached in many cases did not agree with the data from which the decision was made. This was especially true in the forms of those candidates who had a generally unfavorable personality where the tendency was to "pad" the findings to support disqualifications. Thus a candidate with a normal heredity and past history who was dull, vague, untrained, deliberate, careless and slow would assuredly be poor pilot material, but not unnecessarily unstable, yet many such were so called. I believe that this is the explanation for a great part of the lack of correlation between the unstables and the cardiovascular reaction.

If this explanation is not considered valid, then it must be assumed that the best psychologist made the greatest number of errors in the personality studies.

Other minor points which might have contributed to a low correlation is the possibility that first blood pressure-pulse readings were not always recorded on the forms and some cases were probably re-checks, having been examined before, and in either case, the correlation among the unstables would be proportionately low.

In almost all cases of disagreement between the personality classification and the blood pressure-pulse findings it was not because of a slight difference between the findings and the arbitrary limit, but because of a very wide difference, making a widening of the arbitrary blood pressure-pulse range of no benefit, this further emphasizes the fact that the discrepancies are more likely to be an error than that a true correlation does not exist.

The data of Table 2 offer much food for speculation as well as an explanation for much of the inconclusive and controversial work of others.

Among the candidates in this series, 113 (53.3%) were considered stable. They had an average blood pressure of 119/70 and pulse of 80. There can be no doubt that this, being a reaction finding in these individuals, explains, at least in part, the low blood pressures found in most graduate pilots who on subsequent examinations show a more nearly basic reading. This has been especially commented upon in this country by Miller[11] and Green[7] and in England by Threadgold.[17]

There were 12 candidates among the group who were both stable emotionally and at the time of the examination were in active athletic training. Their low average blood pressure of 103/60 and pulse of 74 is in agreement with the findings of Threadgold,[17] Robinson[12] and especially with the work of Adolph Abrahams on track athletes. This should again call our attention to the fact that while a low blood pressure may be a bad omen it can indicate the acme of perfection.

There were 99 (46.7%) of the candidates considered unstable in this group and 5 distinct blood pressure-pulse patterns could be distinguished. Fifty-nine had a high systolic with a normal diastolic and a normal pulse. In these cases the impression was gained that the higher the pulse pressure the greater the relative instability of the individual. In this type it was observed that the systolic would return almost invariably to normal limits if the individual were allowed to return for reëxamination a sufficient number of times and efforts exerted to "calm him down."

Seven candidates were suffering from an essential hypertension and it is significant that all were unstable. In contradistinction to the high systolic group these individuals failed to show a lowered blood pressure under any circumstances and a return for a re-check was always a disappointment; the pulses in all cases were normal.

Another group of 6 candidates also had an essential hypertension combined with a mild degree of tachycardia and except for the pulse rate the observations on this group were the same as for those above.

A second group of 6 candidates showed a high systolic pressure, a high pulse, but a normal diastolic pressure. These were distinguished by the tendency for the systolic pressure to fall on subsequent examinations to normal while the pulse tended to stay high.

The last group of 21 candidates presented a condition which the author feels may in a large measure explain the failure of previous studies to attain a better correlation. These candidates had an average blood pressure of 102/58 as compared to the athletic group mentioned above who had an average of 103/60. Thus from the blood-pressure standpoint there is nothing to distinguish between them. However, the athletic group showed the lowest average pulse (74) while these unstables had an average pulse of 97. Another interesting fact about this latter type of individual is the evident approach of syncope while the blood pressure is being taken as denoted by sweating, palor, cyanosis, and dilation of the pupils. Many of these originally have a systolic which rises far above normal and then suddenly drops, the blood-pressure findings not being definitely established until the wild initial fluctuation has been stabilized at the lower level. These individuals are considered to be the most unstable of all the groups and belong to that class "who can't stand the sight of blood without fainting, can't tolerate pain without nausea or vomiting and are driven to the verge of fainting by the 'peculiar tingling' of the arm and hand and the sickening pain of compression of the cuff on the arm (brachial artery and nerve)" during a blood-pressure reading.

Constituting approximately 21% of the unstable group it is perfectly obvious that investigators who work on the hypothesis that the blood pressure rises in reaction to an emotional stimulus and that the rise is proportionate to the degree of stimulation as measured by introspection, or any other means, are bound to be frustrated by this type of individual. This applies also to those who are dealing with the cardiac rate when, as shown in Table 2, 66% have an average rate comparable to that found in the stable cases.

In view of the above findings it is now possible to understand why Braun[4] found it necessary to point out the fallacy of the statistical method of correlating psychic complaints and cardiac disorders and recommended studying the heart and mental life of each individual. However, it must be pointed out that his theory that anxiety is located in the cardiac tissue does not explain the fact that in the present study the majority of the cardiovascular reactions are on the blood-pressure side and not on the cardiac side, unless we wish to admit that those candidates who were of the anxious type reacted only by high pulse rates.

The failure of Scott[15] and of Landis and Gullette[8] to find a correlation between the degree of emotion and the degree of blood-pressure change is probably due to the fact demonstrated above, that the blood pressure is not always the part of the cardiovascular system which reacts, and in any event does not react in all cases to the amount of stimulus but more nearly according to the relative stability of the individual.

This leads us to speculation as to the causes of the different patterns found in the unstable group. Either it must be assumed that Braun's[4] theory, extended to cover all emotions, is correct, or we must assume that each pattern is but a quantative measure of the relative instability.

If we accept Braun's[4] theory that the heart is the organ of anxiety, then we must likewise assume some organ to be the center for anger, *fear, hate, love, resentment, embarrassment and all of the other* emotions. If each of these does not have a specific organ as a center (which seems quite unlikely) then we must assume that several are associated in one organ and the reaction of that organ must depend on either the reaction of the emotion elicited or the sum-reaction of all its emotions which, in any event, involves tissues such as the adrenals (in anger), the hair (in fear) and others which are controlled by the central nervous system and not by the cardiovascular system.

It seems much more reasonable to assume that the different cardiovascular patterns noted are quantative reactions modified in some cases by physiologic considerations.

The athletic group maintain a nearly basic blood pressure and pulse, which are supported by an efficient physiologic reserve of power to meet an emergency, a reserve not dissipated by an unnecessary anticipatory rise to meet a harmless emotional situation. The normal group reacts mildly to the emotional stimulus by a rise in the systolic blood pressure.

In the relatively unstable group the first evidence is a relatively high systolic blood pressure, which being the most sensitive to emotional stimuli is the first to react beyond the normal. In the next stage, the pulse reacts to join the systolic rise, while the stolid systolic blood pressure still retains its normal level; or the finding may be reversed with the diastolic rising with the systolic while the pulse retains its normal level. Then comes the group with the diastolic blood pressure and the pulse joining the high systolic as the whole cardiovascular system is reacting together.

The final group is composed of those who would react to the highest degree but lack the necessary physiologic equipment to carry out the required response and the blood pressure rises then drops with dramatic rapidity leaving only the heart struggling vainly with thready pulse to maintain the defense of the organism.

Before concluding, it is desirable to point out that the use of this proposed test of emotional stability in its present incomplete state has many shortcomings and is limited in its application. It is probably valueless for use with neurotic and psychotic patients as shown by the work of Threadgold[17] and Gillespie.[6b] It is only useful on an original examination and cannot be repeated because upon reëxamination, the examiner and the environment being no longer strange, the stimulus is lessened. However, in this connection, it must be remembered that unless basic blood-pressure and pulse levels are determined during sleep or after medication that a reaction to any other emotional stimulus is superimposed on the stimulus of the examination and in the end must depend in part on the latter.

The arbitrary blood pressure-pulse limits used in this study probably do not apply to all age groups, even among adults, or to both sexes, since it has been shown that with increasing age the reaction of the cardiovascular system decreases and in the female sex the cardiac rate reacts to a greater extent than in the male. Therefore this test is probably only valid for the conditions stated in the study. For any other use it would seem advisable to extend this study to apply to the age groups and sexes to be examined, to standardize examination procedures used, and to decide on the degree of emotional reaction to be considered abnormal. For agencies or concerns who have a large personnel and who desire an insight into their emotional as well as their physical status by the simple process of a routine physical examination, such a further study seems well worth while.

Summary. A review of 700 examinations of candidates for flying training for the United States Army Air Corps shows that there is a correlation of .98 for the stable group and .88 for the unstable group and a general correlation of .92 between the relative emotional stability of the individuals and their cardiovascular findings.

This correlation was obtained by adopting an arbitrary blood-pressure level of 134/90 (+ or −3) and a pulse rate of 90 (+ or −3) and assuming that any reading above that level demonstrated a relative emotional instability.

The failures of previous workers to demonstrate a high degree of correlation between emotional stimuli and cardiovascular reactions and certain other inconclusive evidence and disagreements in the literature is explained by an analysis of the reaction-patterns of the author's cases into 5 distinct groups, wherein it was shown that among the unstable candidates 21% showed no abnormal blood pressure pattern and 66% showed no abnormal pulse pattern. These dissimilar reaction patterns show the fallacy of mass statistics in such studies and demonstrate the necessity of studying the cardiovascular system as a whole in each individual in psychosomatic investigations.

The limitations and shortcoming of the described test for emotional stability are pointed out, as well as a suggestion for further studies which are necessary before the test is applicable to any situation other than the one from which the test was derived.

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GASTRIC ACIDITY AFTER GASTRO-ENTEROSTOMY.

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Investigation of the chemical physiology of the operated stomach has led to a wide variety of results. Frequently these various findings have been used as a basis for the development and use of one or another type of surgical therapy, and occasionally superiority is claimed for a particular procedure on questionable evidence. The simple posterior gastro-enterostomy has long been the center of a storm of controversy, proponents claiming and opponents denying its ability to reduce the gastric acidity. This wide difference of opinion immediately suggests fundamental limitations in the methods used in determining the postoperative gastric acidity that necessarily preclude uniform results.

Bloomfield and Keefer[4] have raised definite objections to the commonly used type of test meal and have emphasized that the effect of the variable factor, namely, the speed of gastric emptying, must be reduced to a minimum. They have pointed out that the acidity values obtained from specimens aspirated from the stomach after the administration of a test meal vary with the unknown factor of the speed of gastric emptying, and that great variations in the hydrochloric acid values are obtained simply as the result of neutralization by gastric contents.

The factor of emptying time is even more variable in the postoperative stomach because of the abnormal mechanics present and because of the gastro-enteric stoma, which provides both an additional outlet for stomach contents and an inlet that favors a more constant regurgitation of duodenal contents. A standardized procedure that insures an empty stomach secreting pure gastric juice as a result of a powerful stimulus reduces to a minimum the error caused by the variability of the emptying time and sets the stage for a true analysis of the gastric secretions.

This paper is based upon a study of the gastric secretion of 75 patients with peptic ulcer, all of whom had been treated by posterior gastro-enterostomy.

Literature. In reviewing the literature on the subject of postoperative acidity, one finds that there is a surprising lack of agreement among the various authors, though the majority agree that gastro-enterostomy results in considerable reduction in the gastric acidity. The reports may roughly be divided into three types:

First, the reports that cite no gastric acidity figures. Many authors[1,5,6,37,41,46,50] state that the acidity is lowered; a lesser number maintains that there is no appreciable change.[10,20,24,35]

Second, those that cite average mean figures on a group of patients. Although there is considerable variation in the results obtained, there is general agreement that the postoperative gastric acidity is reduced by from 30% to 60% following gastro-enterostomy.[2,17,28,29,33,44,53,55,57,58,60,62]

Third, those that either segregate their results in relation to normal gastric acidity or cite figures for each patient. Again, most of the authors find that the acidity is reduced in the majority of cases, but dissenting opinion is strong and would be convincing if it were based on a larger number of cases. In Tables 1 and 2 results of these more detailed studies are listed. The findings are divided according to the degree of acidity and are based on the commonly accepted figures obtained in an Ewald meal or one of its modifications, *i.e.*, 0°–20° free hydrochloric acid as subnormal, 21°–45° as normal, and 45° or higher as hyperacidity. Those cases in which added procedures, such as excision of the ulcer, pyloric occlusion, and entero-enterostomy, were undertaken have been excluded from the figures given in Tables 1 and 2, although the various authors have reported them as having had a gastro-enterostomy. As a result, the total number of cases, as tabulated, may show minor variations from the original reports from which they were assembled.

The following discussion concerns itself only with the more detailed reports as listed in Tables 1 and 2.

Table 1 lists the authors who have found a definite diminution in the postoperative acidity. With the exception of Sherren,[52] all the authors find approximately the same results. However, it may be well to explain why Kramer,[31] Kreuzer,[32] and Wydler[63] have been placed in this group even though they state that gastro-enterostomy results in little lasting change in the gastric acidity. Analysis of their postoperative observations reveals that Kramer found that 35%, and that Wydler and Kreuzer found that over 50% of the patients had a subnormal or absent acidity. Kramer is of the opinion that the reduction of hypersecretion parallels the improvement in the motor function of the stomach, but that the acidity at the height of digestion is not reduced. Kreuzer found that the patients who were examined shortly after operation showed a diminution, in contrast with those studied long after operation, who

TABLE 1.—CASES FROM THE LITERATURE.

Author.	Year.	No. of cases.	Hyper-acidity.	Nor-mal.	Sub-normal.	Anacid-ity.
Carle and Fantino[9]	1898	16	3	6	4	3
Hartman and Soupalt[21]	1899	6	3	..	2	1
Deganello[12]	1900	2	..	..	2	
Kramer[31]	1906	34	10	12	5	7
Kreuzer[32]	1906	26	3	11	12	
Wileox[59]	1909	5	1	..	1	3
Petren[47]	1911	28	9	10	9	
Faulhaber and v. Redwitz[18]	1915	2	1	..	..	1
Nielsen[40]	1919	38	..	..	30	8
Berberieh[3]	1920	35	..	16	4	15
Conybeare[11]	1922	28	6	6	3	13
Wydler[63]	1922	36	4	14	5	13
Hunter[23]	1923	10	6	2	..	2
Sherren[52]	1924	408	38	60	80	230
Ohly[42]	1924	43	11	8	22	2
Devine[13]	1925	19	4	4	2	9
Lindsay[36]	1929	60	19	12	9	20

tended to reach a more normal acid value. Wydler also bases his assumption on repeated studies of the gastric secretion in the same patients; he mentions only 2 cases specifically. From these observations, Kreuzer and Wydler assume that if all cases were studied over several years' time the majority would have normal values. Our findings do not agree with this, as will be shown later. Faulhaber and v. Redwitz[18] maintain that gastro-enterostomy cannot be depended upon to produce an anacidity, although 1 of the 2 cases reported by them showed an absence of free hydrochloric acid. Petren,[47] who states that in over half the cases the acidity is not changed following gastro-enterostomy, is also included in this group of authors, since he found 32% of the patients with subnormal or absent gastric acidity.

Table 2 lists the findings of the authors who show little, if any, reduction in the postoperative gastric acidity. When the results in this group are compared with ours, a striking similarity may be noted. A total of 67 cases reported in the literature since 1898 seems unbelievably small; but it must be remembered that this includes only the reports that give case data. Perman[45] has made some interesting studies on patients who have had both gastro-enterostomy and gastrostomy performed at the same operation. All drainage from the gastrostomy tube was collected in 24-hour

TABLE 2.—CASES FROM THE LITERATURE.

Author.	Year.	No. of cases.	Hyper-acidity.	Nor-mal.	Sub-normal.	Anacid-ity.
Kausch[26]	1899	6	3	3		..
Rencki[48]	1901	14	4	8	2	..
Kindl[27]	1909	5	2	2	1	..
Sehur[51]	1911	12	3	7	2	..
Troell[54]	1911	9	1	7	..	1
Bonar[7]	1921	3	2	1	..	..
Lewisohn and Feldman[34]	1925	11	1	9	1	..
Elman and McLeod[15]	1935	7	2	4	1	..

specimens and the total acid determined. He found that the total acid was equal to, and in some cases greater than, that obtained under similar conditions from patients on whom only a gastrostomy had been performed. Observations were made only until the gastrostomy tube was removed, usually from 5 to 10 days postoperatively, but they furnish conclusive evidence that at least immediately after operation the secretion is not diminished.

With the exception of several reports describing primarily either malfunctioning gastro-enterostomies or anemias following gastro-enterostomy, Tables 1 and 2 represent to our knowledge a complete bibliography of cases reported since 1898. Prior to that time only 8 patients with postoperative gastric studies have been reported.[14,22,30,39,49]

Experimentals. Experiments to determine the effect of gastro-enterostomy on the chemistry of the stomach have resulted in considerable divergence of opinion. The results obtained cannot be entirely accepted as applicable to the human because (1) the mechanisms that regulate gastric acidity in the normal unoperated stomach in both man and animal have not been clearly defined or agreed upon, and (2) the reaction of the normal stomach of experimental animals will not necessarily mirror those of the human diseased ulcer-bearing stomach.

There is no general agreement as to the effects of gastro-enterostomy in the experimental animal, although most investigators find reduction in the gastric acidity.[8,43,61] Wilhelmj, Heinrich, and Hill[61] have made exhaustive studies, using an acid test meal and histamine as a secretagogue. They conclude that the reduction in acidity following gastro-enterostomy is due entirely to regurgitation of duodenal contents, and that the reduction is due more to dilution than to neutralization—on the average 75% by dilution, and 25% by neutralization. They conclude further that the presence of large amounts of duodenal secretion in the stomach postoperatively seems to cause a hypersecretion of acid by the stomach, which is evident only after stimulation by histamine. Katzenstein[25] believes that the reduction of the acidity is due not only to neutralization but also to inhibition of gastric secretion. He considered this proved when, after introducing jejunal contents into the stomach of a dog on which a Pavlow pouch had also been made, he found inhibition of the secretion in the Pavlow pouch. Enderlen, Freudenberg, and v. Redwitz[16] find very little reduction in the acidity, and this they believe is due to an intragastric reduction. They found in experiments *in vitro* that it required four times the amount of a dog's duodenal contents with a pH of 6.98 to neutralize a given amount of stomach contents with a pH of 3.07, the latter corresponding to a relatively low acidity (normal pH value 1.3 to 2.4). Jianu[24] and Wada[56] find the acidity unchanged if repeated examinations are made.

Material and Methods. Satisfactory study of the gastric secretions of the postoperative stomach has been difficult because of the presence of regurgitated duodenal contents. The administration of a test meal of one type or another only increases the difficulty of obtaining pure gastric juice, and, as a result, the mixture obtained gives no idea of what the stomach is actually secreting. To eliminate this source of error we have performed the gastric analysis according to the method of Bloomfield and Polland.[4a]

Seventy-five patients with peptic ulcer were studied, on all of whom a simple posterior gastro-enterostomy had been performed. With 3 exceptions, the Halsted gastro-enterostomy was performed, and the various operators used a standardized technique.[19] The intervals between operation and observation ranged between 6 months and 4 years, and in many instances studies were repeated on the same patients over a period of 2 years. The writers personally investigated and followed each patient instead of using the statistics from the records. The gastric analysis is done after a fast of 12 hours with histamine used as a stimulus in a dose of 0.1 mg. per 10 K. body weight. The fasting contents are withdrawn, the histamine is injected subcutaneously, and then the stomach contents are continuously aspirated and collected for from 3 to 6 10-minute periods. No test meal was introduced into the stomach, and it may be mentioned that no ill effects from the use of histamine were observed. The material was studied from the point of view of its gross appearance, its amount, and the presence of acid and bile. The 10-minute specimen with the greatest 10-minute volume of secretion and the highest titrable acidity is considered the index of gastric function. To insure an accurate determination, certain precautions must be observed: (1) The person performing the aspiration must be familiar with the technique of aspirating a stomach and interested in obtaining accurate results. (2) The stomach must be aspirated absolutely dry before the fractional specimens are collected, and on occasions the test may have to be abandoned for the day because of the constant regurgitation of bile. (3) Dilution of the gastric contents must be avoided if possible, and all heavily bile-containing specimens should be segregated. The importance of following the described procedure in order to obtain an accurate analysis cannot be overemphasized. It has been our experience on numerous occasions that the results obtained by the relatively uninterested technician will not compare with the results of one who is interested in the condition of the patient.

Results. *Character.* The gastric juice is, as a rule, rather clear and frequently discolored by small amounts of bile. In a small number of patients, thick viscous bile was found at all examinations even when they were repeated at long intervals. In a few instances considerable mucus was present. As a rule, the character of the gastric contents is the same on repeated examination.

Volume. The average volume for the 75 cases before and after operation is practically the same—52 cc., and 55 cc., respectively. However, in the individual patient the volume is seldom the same after operation as it was before, and in this group there was an equal number of patients with higher and lower postoperative volumes. The wide variations are striking and make it evident that no narrow standards can be set up, but in a general way the higher volumes are associated with the higher acidities. We could find no relation between the clinical result and the volume, nor did we find that the amounts of bile in the aspirated juice corresponded in any way to the volume.

Acidity. In Chart I, the solid line connects the free hydrochloric acidity value of each of the 75 cases, recorded in the order of their degree of acidity. There is little variation in the difference between the free and the total acidities, the latter averaging about 10 degrees higher than the free hydrochloric acid.

Sixty-nine (92%) of the patients had acidity (free hydrochloric acid) higher than or within normal limits (60 degrees of free hydrochloric acid or higher), and 6 (8%) had subnormal or anacidity (less than 60 degrees free hydrochloric acid). Only 1 patient had a complete absence of free hydrochloric acid. For the 75 patients, the average postoperative acidity was 82 degrees free hydrochloric acid. If the 6 cases in the subnormal acid group are not included, the average postoperative acidity for the 69 patients in the normal acid group is 88 degrees.

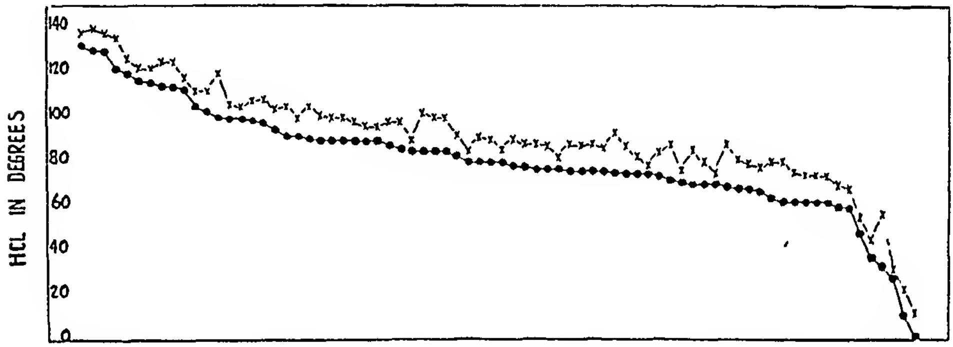

Chart I.—Hydrochloric acidity in 75 cases. Postoperative acidity. Crosses = total HCl. Dots = free HCl.

A glance at the distribution curve (Chart I) immediately suggests that the 6 patients with subnormal acidity may be considered as a distinct group apart from the patients with normal or high acidities. From 3 to 6 analyses over a year's time were performed on each of the 6 patients in the subnormal acid group, and the results of the various examinations were always within 15 degrees. The confirmatory results of the repeated examinations are adequate evidence that there is a small percentage of patients who have a definite subnormal acidity following gastro-enterostomy. In the subnormal acid group the volumes were lower than in the normal acid group, and the character of the aspirated juice was different. The constant findings of low acid and low volumes place the former in a distinct group. This altered gastric secretion can probably not be explained simply by regurgitation of duodenal contents. Gastritis may conceivably be an etiologic factor but its presence can be determined only by pathologic examination. Advances in gastroscopic investigation may lead to more definite conclusions.

Fifty of the patients had similarly performed preoperative gastric analyses (Chart II). The number of preoperative acidities that were higher than the postoperative acidity is practically the same as the number that were lower. To be sure, most of these differences can be explained by the limits of error of the test, but also the operated stomach may predispose to functional changes in the gastric secretory mechanism. Possibly improvement in the gastric function following operation may be reflected by an increased secretory function of the stomach. This is supported by our findings in the small number of patients who have unsatisfactory clinical results following gastro-enterostomy. In none of the latter patients was the postoperative acidity greater than the preoperative acidity.

In Chart III, the preoperative and postoperative free hydrochloric acid values are charted in descending order, the dots representing the postoperative acidities and the crosses the preoperative acidities. It must be emphasized that this chart illustrates the distribution curve of a group of cases; the dots and crosses do not represent corresponding patients as they do in Chart II. The distribution curves for the preoperative and postoperative acidities are practically the same except for the small group of patients who have low free hydrochloric acid following gastro-enterostomy. The average preoperative acidity for the 50 patients was 90 degrees; excluding the 5 patients in the subnormal group, the average postoperative acidity was 88 degrees.

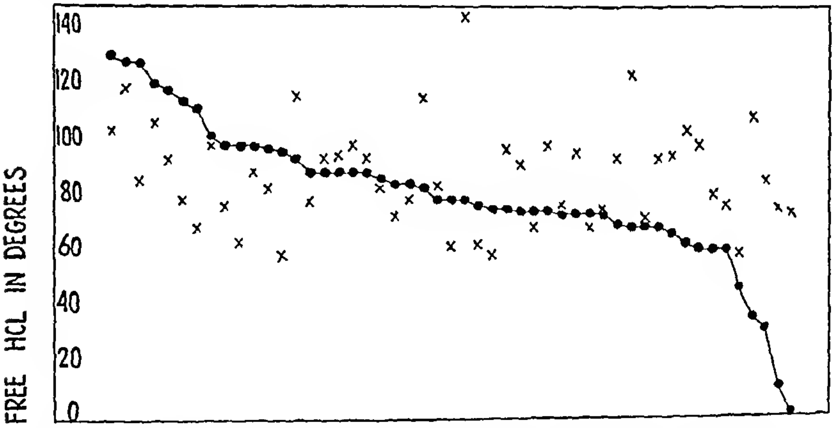

Chart II.—Preoperative and postoperative acidity in 50 cases. Crosses = preoperative acidity. Dots = postoperative acidity.

The patients with preoperative pyloric obstruction comprised slightly more than half of the 75 patients. Chart IV shows that the postoperative acidity values are not influenced by the presence of preoperative pyloric obstruction.

On 68 of the patients, postoperative roentgenograms of the stomach were obtained. Three of these were reported as unsatisfactory, *i. e.*, 2 suggestive of marginal ulcer and 1 an overactive stomach. The acidity in these 3 cases ranged from 55 to 130 degrees free hydrochloric acid. If the patients are divided into two groups, those with and those without pyloric emptying by Roentgen ray, the average acidity in the latter is about 12 degrees less than that in patients who had pyloric emptying. This difference is difficult to explain, particularly when one considers that the presence of preoperative pyloric obstruction in no way influenced the postoperative acidity.

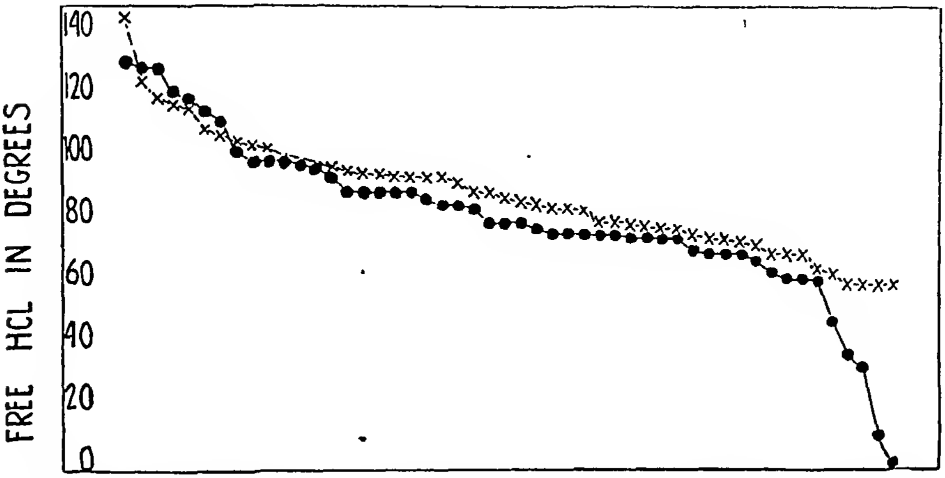

Chart III.—Preoperative and postoperative acidity, both arranged in descending order. Crosses = preoperative acidity. Dots = postoperative acidity.

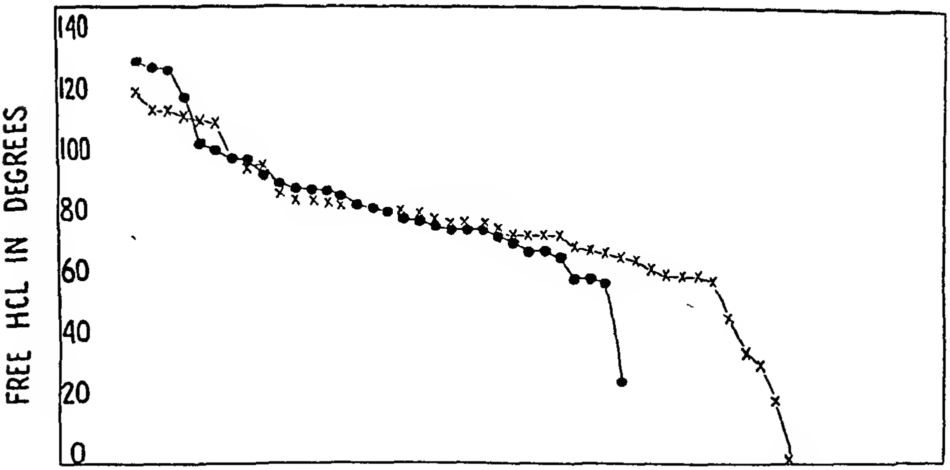

Chart IV.—Postoperative acidity with regard to preoperative obstruction. Crosses = cases with obstruction preoperatively. Dots = cases with no obstruction preoperatively.

The amount of bile present in the aspirated juice has no relation to the acidity in this group of patients. The amount of bile present may be assumed to give some idea of the quantity of duodenal regurgitation, although, as emphasized by Medes and Wright,[38] trypsin may be present in the stomach in the absence of bile.

The interval of time between operation and the postoperative analysis has been said to influence the secretion of the stomach. Of the 25 patients with the highest acidities, there is an equal number of patients with a postoperative interval of less than 1 year and of more than 3 years. Likewise, the acidity is not influenced by the time interval in the group of 25 patients with the lowest acidities. On 30 patients repeated postoperative examinations were made and, although there were slight variations in the acidities obtained in most cases, only 3 patients showed marked changes; in 2 of these the acidity had decreased and in the other the acidity had increased over a 2-year period. Two of these patients had variations of about 40 degrees, but at all times the acidity remained above 75 degrees. The third patient had a reduction in acidity from 90 to 60 degrees; 4 recent examinations confirm this reduction. During this time he has had no change in symptomatology, and since his operation he has had no complaints.

Although for the majority of these patients, less than 5 years have elapsed since the time of operation, it is interesting to correlate the clinical result with the acidity. In the future, the clinical result may change in a certain number of these patients, but it is hard to believe that this number will be large enough to alter the significance of our findings. To insure a true statistical picture, we have charted the result against the acidity in several combinations, and in this group of cases we have been unable to find any correlation between the clinical result and the acidity. The 6 patients with a subnormal acidity have had satisfactory results up to the present time. Fourteen patients have been classified as having unsatisfactory results and in these the acidities ranged from 55 to 130 degrees free hydrochloric acid. In the 61 patients with satisfactory results the acidities ranged from 0 to 132 degrees free hydrochloric acid.

Investigation of the ethnic influence reveals that all races, except the Jewish, are distributed widely over the range of acidity. Although the number is too small to be conclusive, all 14 Jewish patients had an acidity above 70 degrees.

There is a tendency for the acidity to diminish slightly with advancing years. This is by no means so apparent as in a group of normal individuals.

In our experience the postoperative acidity has not been influenced by such factors as the activity of the ulcer at the time of operation, the duration of symptoms before operation, or the symptomatology and clinical findings before operation.

Discussion. The purpose of the present work has been to determine standards for the gastric acidity of peptic ulcer patients on whom a simple posterior gastro-enterostomy has been performed. The literature on which the present concept of the postoperative gastric acidity is based has been analyzed in detail. In all previous studies the Ewald meal or one of its modifications has been used and has led to a wide variety of results. To obtain accurate results, however, it is necessary to use a standardized procedure, the results of which are not influenced by unknown variables as are the results of the ordinary test meal.

In 92% of the 75 patients investigated the gastric acidity was not appreciably altered by gastro-enterostomy. In 8% the acidity was diminished to below normal, but in only 1 patient did it reach a complete anacidity. That there is an actual decrease in acid secretion in the latter group is supported by the associated low volume obtained in these cases.

These findings lead to speculation as to the cause of the therapeutic effect of gastro-enterostomy. It would seem that some factor other than the alteration of the gastric acidity is responsible for the relief derived from operation.

From the clinical standpoint one is interested in the practical value of such findings. These results do not support the statement, so often found in the literature, that a high gastric acidity lessens the chance for obtaining a satisfactory result from gastro-enterostomy. Furthermore, until the therapeutic function of a gastro-enterostomy is more clearly understood, one may expect a better result from the operation if it is considered, not as the complete and final treatment for a patient with peptic ulcer, but as an additional therapeutic measure to be undertaken in connection with other therapy.

It will be interesting to investigate the subnormal acid group of patients in the future to determine whether the acidity returns to normal or gradually decreases to complete anacidity. Whether carcinoma or anemia is more likely to develop in these patients can be answered only after continued observation.

Summary. 1. A detailed analysis of the literature on postoperative gastric acidity reveals a wide variety of results, which suggests fundamental limitations in the methods of investigation.

2. Standards were determined for the gastric acidity of patients with peptic ulcers on whom a simple posterior gastro-enterostomy has been performed. It was found that the gastric acidity was not appreciably altered by gastro-enterostomy in 92% of the 75 patients investigated.

3. The degree of preoperative or postoperative acidity cannot be used in the prognosis of the therapeutic effect of gastro-enterostomy.

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THE INFLUENCE OF FILLING THE STOMACH ON THE COLON MOTILITY AND DEFECATION IN THE DOG.*

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Holzknecht[3] observed mass movements in the colon shortly after the feeding of a bismuth meal. Hertz[2] noted the mass movements of Holzknecht and also observed that the sight of food seemed to initiate the same type of motility. His conclusion, however, was that the entry of food into the stomach seemed to be the chief stimulus for the initiation of the mass movement and he therefore termed the phenomenon the "gastro-colic reflex."

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* A preliminary report of this work appeared in the Proceedings of the American Physiological Society (Am. J. Physiol., **119**, 312, 1937).

Welch and Plant[7] were able to produce an augmentation of colon activity in dogs and humans in response to feeding but never when food was introduced by way of a gastrostomy. In their opinion, the term "gastro-colic reflex" is a misnomer and the phenomenon should be designated a "feeding reflex."

The procedures used by Holzknecht[3] and by Hertz[2] do not permit differentiation between the importance of feeding and filling the stomach in eliciting mass peristalsis. The observations of Cannon[1] that a close relationship exists between the ingestion of food and defecation fails to distinguish the conception of a gastro-colic reflex from that of a feeding reflex.

Ivy is quoted by Pearcy and Van Liere[4] as having found that the gastro-colic reflex is really a duodeno-colon reflex, at least in the dog, for stimulation of the duodenum and upper jejunum caused defecation, whereas distention of the stomach never had such an effect.

Our work was divided into two parts: first, the effect of filling the stomach with fluid on the motility of the colon; and, second, the defecation response to similarly filling the stomach or distending it with a balloon.

The first study was made on cecostomized dogs which were trained to lie quietly upon a table with a stomach tube in place by way of the esophagus. The tandem balloon system of Templeton and Bollens[5] was used. Motility was recorded for 400 minutes with one set of balloons inserted by way of the cecostomy and the other inserted by way of the anus according to the technique described by Templeton and Lawson.[6] The records obtained represented the degree of motility simultaneously occurring in six segments of the colon. The average segment activity was then computed on a quantitative basis for each 50-minute period. To make this calculation two arbitrary rules were followed. First, a segment was considered active if a contraction or contractions lasted for 1 minute or more; second, a segment was considered quiet if 2 or more minutes intervened between contractions. No attempt was made to measure the strength of activity as indicated by the height of contractions on the tracing.

Seventeen experiments were conducted on 2 dogs. At the end of 200 minutes in 8 of these experiments a mixture of one-half pound of yeast and approximately 1100 cc. of buttermilk was administered by way of the stomach tube without interrupting the tracing. Nine of the experiments were continued as controls throughout the 400 minutes without experimental intervention. The average activity in the first 200 minutes (Fig. 1) of all the experiments varied from 41 to 47% per 50-minute period. In those continued as controls, the average activity in the second 200 minutes was less than the grand average of all of the experiments during the first 200 minutes and varied from 39 to 43% per 50-minute period. The filling of the stomach with the yeast and buttermilk mixture was followed by an increase in colon activity which began during the first 50 minutes after the injection and had not reached a peak at the close of the experiment 200 minutes later. The activity rose from 41 to 74% during this period.

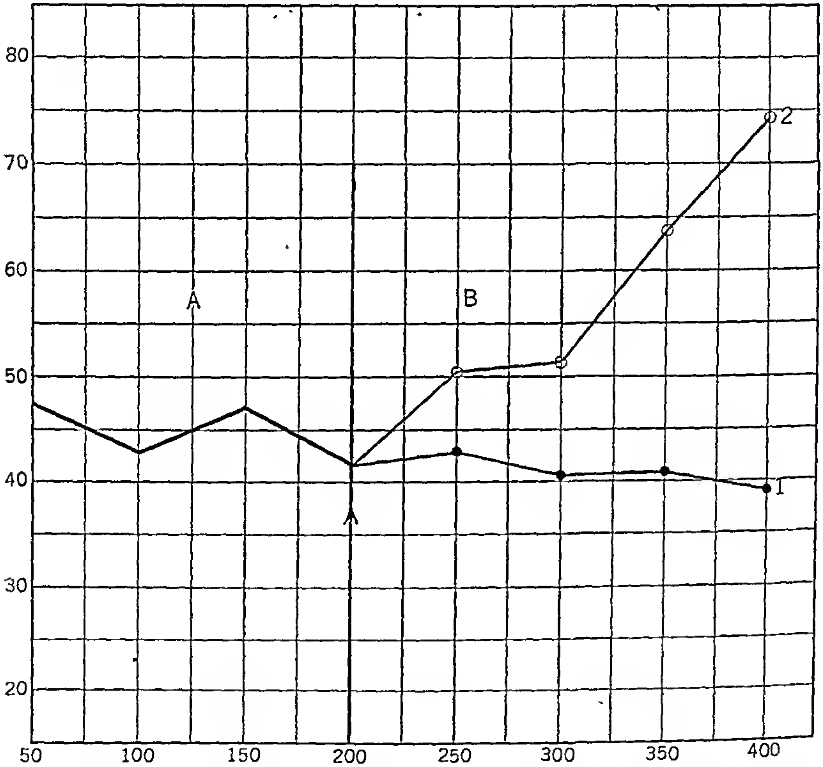

FIG. 1.—Part A represents the average per cent of activity in the 200-minute control period for all (17) experiments; Part B, in the 200-minutes following the control period. Curve 1 (Part B) represents the average per cent of activity in the 9 control experiments; Curve 2 (Part B), in the 8 experiments following the filling of the stomach with one-half pound of yeast and 1100 cc. of buttermilk.

In the second study, where the index of response to the filling of the stomach was defecation, 14 animals were used. Of these animals, 11 were untrained and recently obtained from the pound and 3 were house-broken and had been under laboratory environment for a year or more. In 32 experiments on the untrained dogs failure of defecation occurred in only 9 instances. These were all attributable to the inability of the animals to retain the mixture. When vomiting did not occur defecation was elicited immediately (usually within 1 minute) following the administration of the yeast-buttermilk mixture by way of a stomach tube.

The three trained animals did not defecate following the filling of the stomach in the laboratory room where the experiments were at first being conducted. One of these animals was later studied in another room where the animals were accustomed to defecate. Under these conditions the filling of the stomach was invariably followed by defecation, except when visitors were permitted to observe.

Gastrostomies were performed on 3 of the untrained animals which had previously responded with defecation upon filling the stomach by way of the esophagus. After allowing 2 weeks for recovery the yeast and buttermilk mixture was given by way of the gastrostomy. In every instance defecation followed as quickly as when the stomach was filled by way of the esophagus.

Since the material used in all of the experiments was fluid in nature, it seemed possible that some of it might be rapidly ejected from the stomach into the duodenum and thus elicit the duodeno-colon reflex suggested by Ivy. To study this mechanism further, a balloon was inserted by way of the gastrostomy in each of the dogs that had previously responded with defecation to the filling of the stomach with the yeast-buttermilk mixture. The balloons were distended with 1100 cc. of air under 20 mm. of mercury pressure. Each animal was then rapidly bandaged with the inflated balloon left in place. Defecation was observed within 1 minute in all cases upon release of the animal.

Summary. 1. Colon motility is augmented in dogs by filling the stomach with a mixture of one-half pound of yeast and 1100 cc. of buttermilk.

2. Defecation is elicited in untrained animals by filling the stomach with a yeast and buttermilk mixture.

3. In trained animals, defecation is elicited only when the environment is suitable.

4. Distention of the stomach with a balloon is as effective in eliciting defecation in untrained animals as filling the stomach with a yeast and buttermilk mixture.

The authors are indebted to Dr. A. J. Carlson who made possible this study.

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THE EFFECT OF ZINC CONTENT UPON THE ACTION OF INSULINS.

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It has been shown previously[1] that crystalline insulin (Stearns) has a more gradual and prolonged effect upon the blood sugar of diabetic patients than does standard commercial insulin; moreover, that by its use the diabetes of the patients could be controlled with fewer doses and fewer units. Similar results have been reported by Freund and Adler[2] and by Mains and McMullen.[3]

Rabinowitch and his collaborators[4] also confirmed these findings but attributed the prolonged action of crystalline insulin to the zinc content thereof, for Scott and Fisher[6] pointed out that zinc is present in crystalline insulin.

In order to determine whether or not the presence of zinc in crystalline insulin is responsible for the prolongation of its action and its efficiency in the treatment of diabetes, this investigation was undertaken.

The effect of standard insulin (Stearns) was compared with that of standard insulin to which zinc had been added; also, the effects of these two preparations were compared with that of crystalline insulin and with that of another solution of Stearns insulin crystals with a very low zinc content.

For the purpose of clarity, these preparations* will be designated as follows:

(A) Standard commercial insulin (Stearns) which has a zinc content of 0.02 to 0.05 mg. per 100 units.[5]

(B) The same commercial preparation to which enough zinc has been added to bring about a concentration of 1.2 mg. of zinc per 1000 units.

(C) Crystalline insulin which had been used in the previous clinical investigation and which was shown to contain 0.8 to 0.9 mg. zinc per 1000 units.

(D) A crystalline insulin preparation with a zinc content of only 0.25 mg. per 1000 units.

In these studies, the minimum maintenance dose of (C) was determined and compared with the same dose of (A), (B) and of (D).

Our experience in comparing various insulin solutions has led to the conclusion that the most equitable basis of comparison is the minimum maintenance dose. This represents the maximum glucose equivalent of the insulin studied, and thus is avoided the possible error of comparing the minimum glucose equivalent of one insulin with the maximum glucose equivalent of another. Inasmuch as it was shown previously that the minimum maintenance dose of crystalline insulin is less than that of standard insulin, the former was used for comparison with an equal dosage of the other insulin solutions.

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* Prepared by Dr. Melville Sahyun, Director of the Biochemical Laboratories of Frederick Stearns & Co.

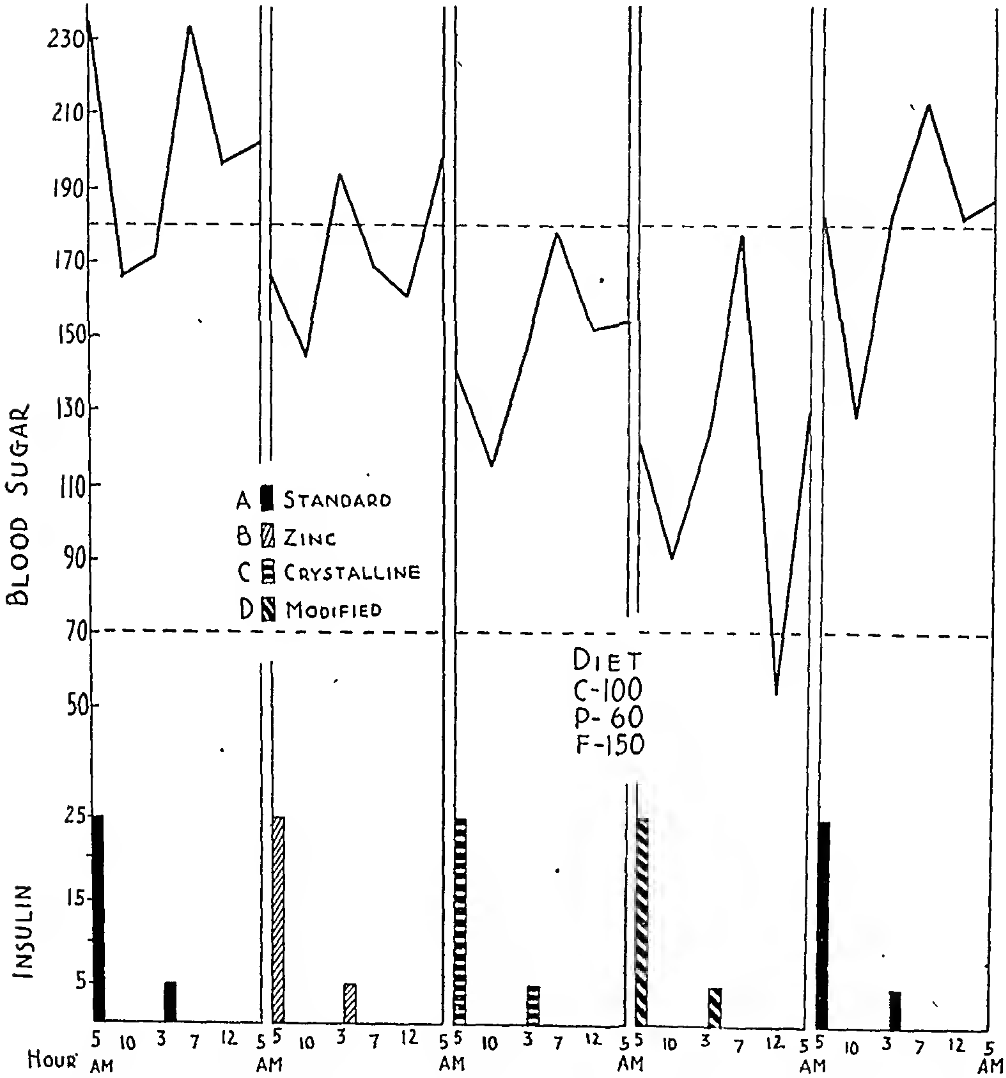

FIG. 1.—Female, aged 50, admitted October 4, 1935. The minimum maintenance dose with crystalline insulin (*C*) was 30 units divided into 2 doses—25 and 5. When (*A*) or (*B*) were given in this dosage, the blood sugar curves ascended to hyperglycemic levels, although with (*C*) or (*D*) they remained within the control limits.

Each of the four preparations was used in the treatment of 11 diabetic patients. All of these patients were hospitalized and most of them had been under observation for more than a year.

Six samples of blood were withdrawn for sugar analysis during a 24-hour period, in each case only after the patient had remained on a constant insulin regime for 1 week. The criteria of diabetes control were blood sugars ranging between 70 and 180 mg. per 100 cc. Values less than 70 mg. were considered the level of insulin reaction, and those above 180 mg., the level of glycosuria. The accompanying charts (Figs. 1 to 5) represent characteristic blood sugar curves obtained in these studies.

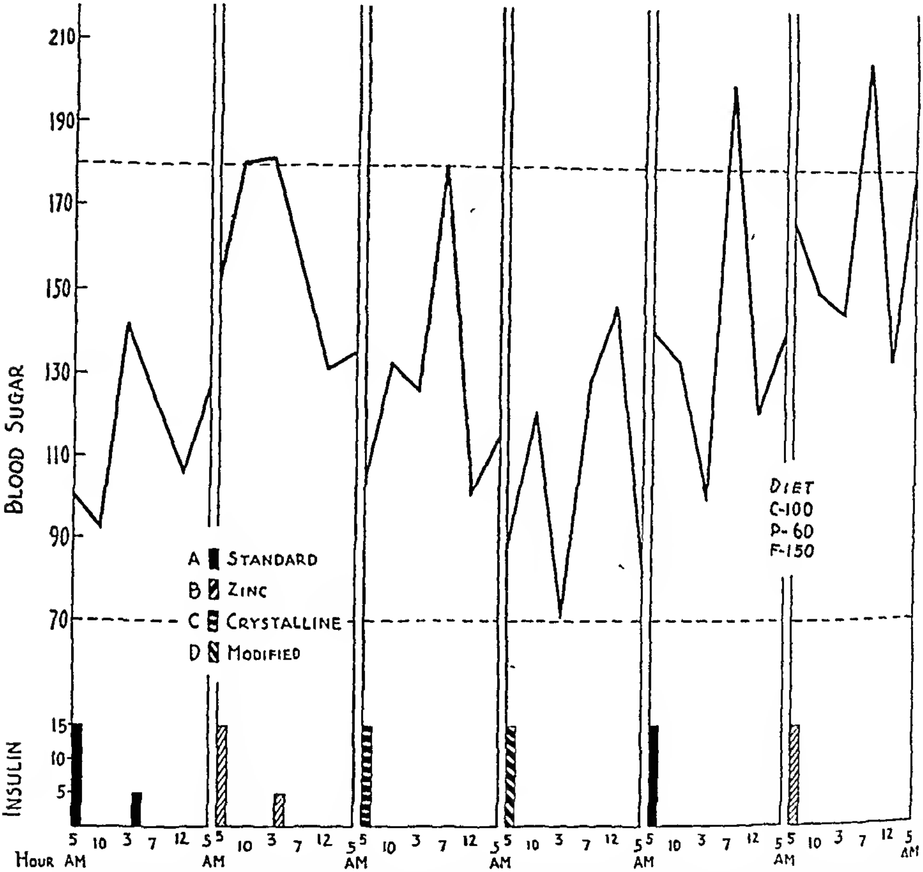

FIG. 2.—Female, aged 57, admitted April 18, 1936. The blood sugar level in this patient was controlled with 15–0–5 units of (*A*) and not quite as well with the same dosage of (*B*). However, with (*C*) and (*D*), 15 units in one dose provided adequate control. Fifteen units of (*A*) or (*B*) proved inadequate.

Analysis of the blood sugar curves obtained in this study showed that the effect of (*B*) was similar to that of (*A*); and that the same patients when receiving (*C*) or (*D*) were better controlled with fewer doses and fewer units of insulin than they had been with (*A*) or (*B*). Finally, a comparison between (*C*) and (*D*) on these same patients showed that (*D*) was as efficient as (*C*) and that in some instances it was even more effective.

Summary. The blood sugar lowering action of four insulin preparations, each one containing an amount of zinc different from the others, was studied in diabetic patients.

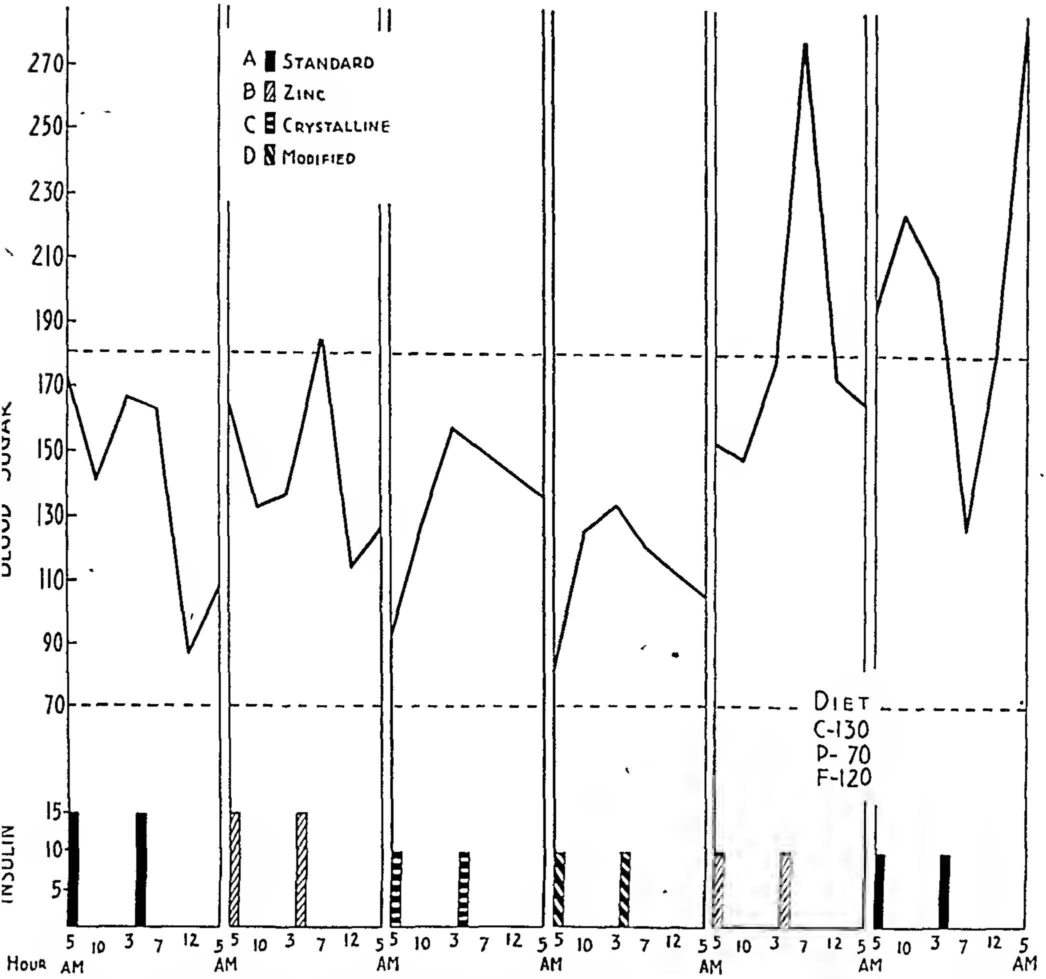

Fig. 3.—Male, aged 47, admitted February 27, 1932. The blood sugar level in this patient was controlled by 30 units of (*A*) or (*B*) divided into two equal doses. With (*C*) or (*D*), 20 units in two equal doses was sufficient. When this latter dosage was used with (*A*) or with (*B*), the blood sugar values rose to hyperglycemic levels.

Analysis of the blood sugar curves obtained in this study shows:

1. That the addition to standard insulin of approximately 1.2 mg. of zinc per 1000 units did not significantly alter the action upon the blood sugar curve.
2. That crystalline insulin (*C*) containing 0.8 to 0.9 mg. zinc per 1000 units as well as a solution of crystalline insulin (*D*) containing

0.25 mg. zinc per 1000 units allowed better control with fewer doses and fewer units than when either standard commercial insulin (*A*)

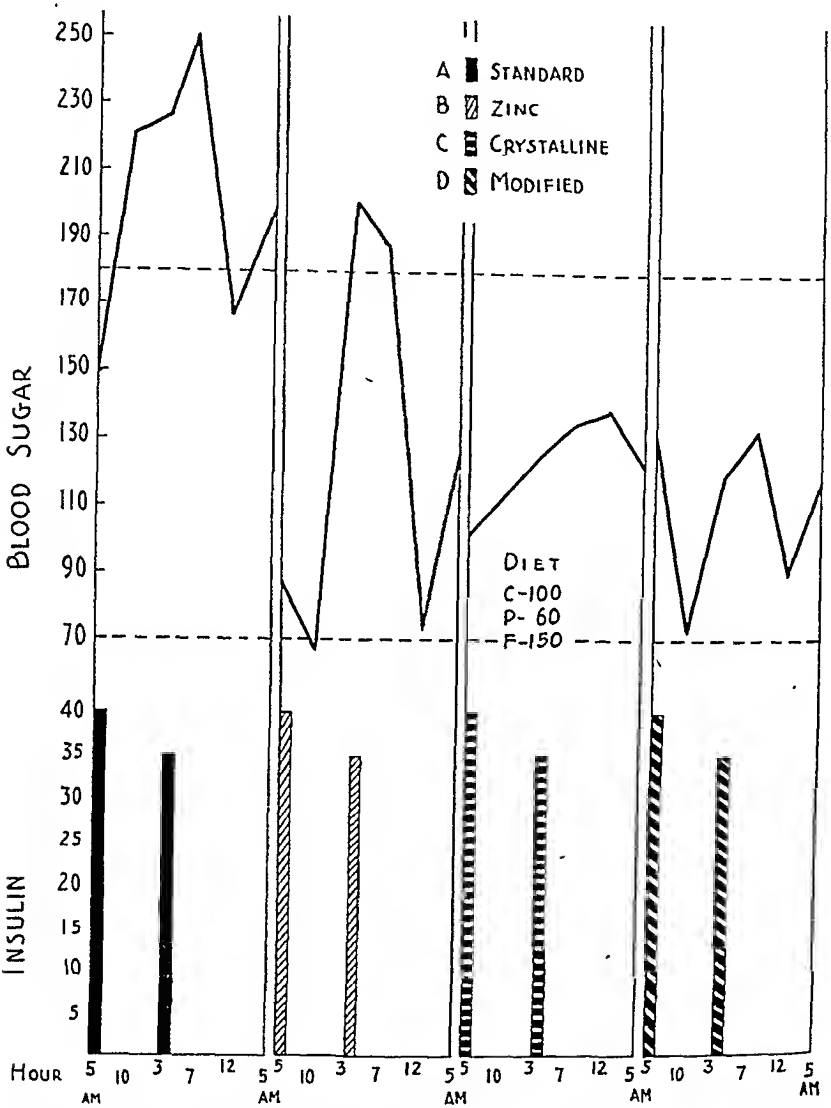

FIG. 4.—Female, aged 50, admitted September 19, 1936. This patient's minimum maintenance dose of crystalline insulin (*C*) had been determined as 40–0–35. A comparison of the effects of this dosage in each of the four different insulins showed hyperglycemic levels with (*A*); a more controlled curve with (*B*) and complete control with (*C*) or (*D*).

or standard commercial insulin to which zinc had been added (*B*) were used.

3. That the solution of crystalline insulin containing only 0.25 mg. zinc per 1000 units (*D*) exerted an action upon the blood sugar at

least equivalent to that of crystalline insulin (*C*); indeed, in some instances (*D*) was even more effective than (*C*).

Conclusion. From the above data it would seem that the prolonged action of crystalline insulin cannot be attributed entirely to its zinc content.

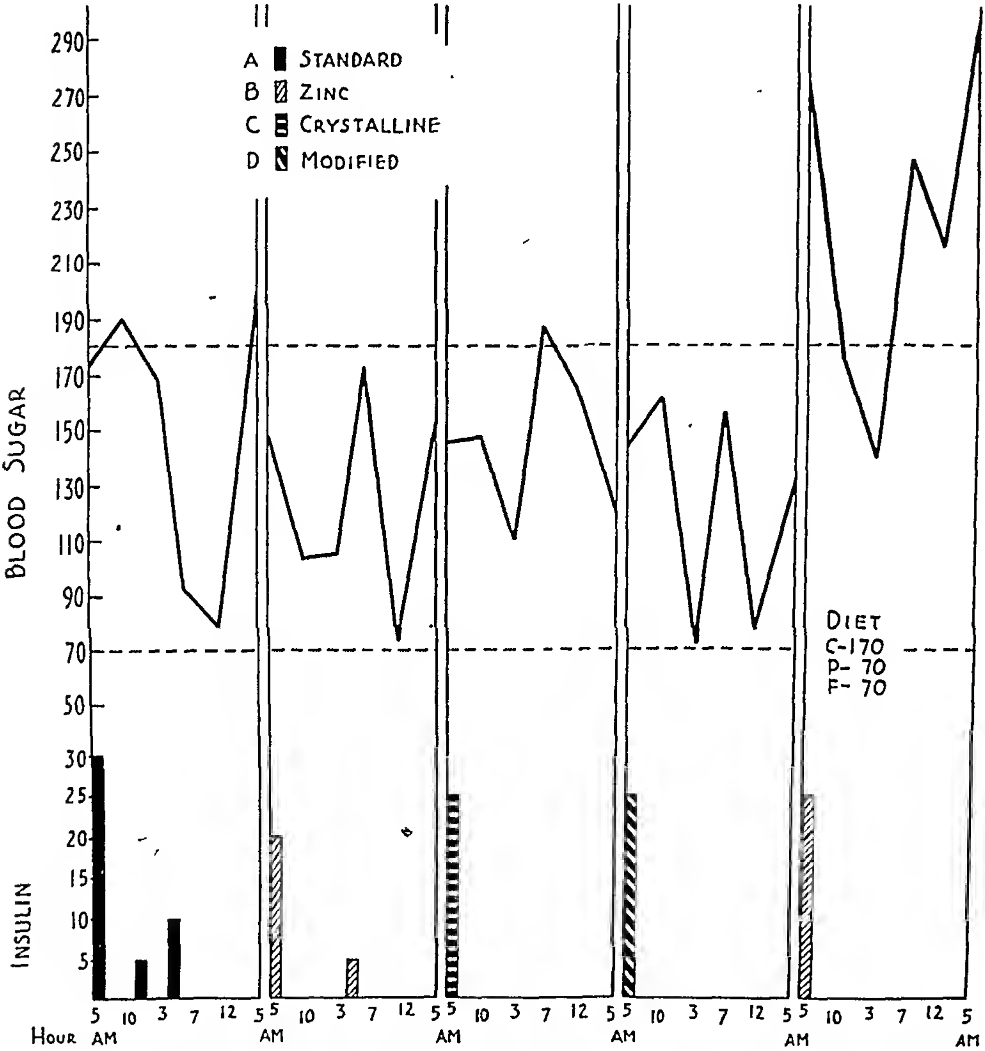

FIG. 5.—Male, aged 50, admitted July, 1932. This patient is extremely sensitive to insulin. His minimum maintenance dose with (*A*) was 30–5–10; with (*B*), 20–0–5; with (*C*) or (*D*) 25–0–0. When 25–0–0 of (*B*) was given, the blood sugar curve rose to hyperglycemic levels.

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OCCULT CARDIOVASCULAR SYPHILIS.*

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We have been impressed by the large number of patients who are found to have cardiovascular syphilis and yet who have come to the clinic entirely unaware of the fact that they have heart trouble. Moreover, in early cases the condition has usually not been recognized by the referring physician. Many of these patients have no cardiac symptoms, and those with symptoms are sometimes found to have only minor physical findings. It is not necessary here to present statistics of the frequency of cardiovascular syphilis. It is a well-known fact that syphilis is today one of the three great causes of cardiovascular disease, being second only to rheumatic fever and senile degenerative changes. And of these three causes, it is the only one for which preventive measures are known and available.

The fully developed syndromes of aneurysm and aortic regurgitation are usually readily detected clinically, but unfortunately the diagnosis of the disease at these late stages is of relatively little benefit to the patient. The important point in cardiovascular syphilis, just as in many other conditions is diagnosis in early stages while the condition is still amenable to treatment.

The diagnosis of cardiovascular syphilis in its early stages presents considerable difficulty. Allbutt,[1] in 1915, emphasized the importance of a change in the quality of the second sound in the aortic area which he described as a "tympanic second sound," citing Potain's comparison of it to the sound of the tabourka, an Algerian earthen drum. The development of roentgenologic methods of studying intrathoracic lesions, and the development of dependable serologic tests for syphilis, have been of considerable additional value. In 1930, Reid[11] in a study of the clinical records of cases that came to autopsy found that cardiovascular syphilis had been diagnosed before death in only 56%, and furthermore that in one-third of the cases not diagnosed the condition was in an advanced state. Moore *et al.*[8a] in a similar study found that only a small percentage of the cases of uncomplicated aortitis were diagnosed during life. They established adequate criteria for its diagnosis, which are now accepted by the Coöperative Clinical Group for the Study of Syphilis. Maynard[5] has shown that syphilitic aortitis can be diagnosed much earlier than is commonly thought possible, by routine periodic examination of all syphilitic patients in a heart clinic throughout the course of their disease. Grant,[4] Moore,[8b] and Cole[3] have shown that the prognosis in cardiovascular syphilis is better, the earlier antisyphilitic treatment is begun, and that the condition can be arrested by adequate therapy in the majority of cases of uncomplicated aortitis.

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* Studies and Contributions from the Department of Dermatology and Syphilology, University of Michigan Medical School, service of Dr. Udo J. Wile

In this study we wish to present an analysis of the symptoms and physical findings in a series of 210 cases of cardiovascular syphilis, and from this to point out the occult nature of the conditions encountered, and to make suggestions regarding their earlier diagnosis. This paper will be followed by a second one which will consist of a study of the roentgenologic abnormalities found in this series and a correlation between these and the clinical findings.

General Data. The material for this study was obtained from the records of patients examined at the University Hospital during the 7-year period, 1930 through 1936. The majority of these patients were seen by both the Department of Medicine and the Department of Dermatology and Syphilology. For purposes of analysis we have separated the cases studied according to their predominating feature into the following groups:

TABLE 1.

	Number of cases.
Aortitis, uncomplicated	83
Aortitis with insufficiency	66
Aortitis with aneurysm (small, 26; large, 35)	61
Total	210

Uncomplicated Aortitis. The criteria used for the diagnosis of uncomplicated aortitis were similar to those developed by Moore *et al.*[8a]* While we recognize that the early stages of aortitis may present no Roentgen changes, in this series we have included only those cases with demonstrable roentgenologic or gross pathologic evidence of dilatation of the aorta. The dilatation was of slight or moderate degree in this group and in most cases was fusiform in type. The diagnosis of aortic insufficiency was made on the clinical findings of a diastolic murmur at the aortic area, abnormal pulse pressure and Roentgen ray evidence of cardiac enlargement.

There is considerable variation in the use of the term "aneurysm." Some writers use it in the strict sense of a sac; and, as Cole,[3] apply it only to large saclike dilatations of the aorta. On the other hand, Osler[10] in speaking of true aneurysm states "they may be fusiform, cirsoid or sacculated. Aneurysms are usually fusiform, resulting from a uniform dilatation of the vessel, or saccular," and Norris and Landis[9] state "an aneurysm may be defined as any circumscribed or localized expansion or dilatation of the lumen of an artery." We have found a more or less middle course more convenient clinically and in this study have included in the group of aneurysms those cases having either a marked fusiform dilatation of the aorta or actual sacculation, small or large. In our second paper we will attempt to define aneurysm in terms of the roentgenologic findings in accordance with orthodiagrammatic measurements. In the present study, films were available in 190 cases and 156 of these had complete fluoroscopic study with orthodiagram.

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* Diagnostic criteria of uncomplicated syphilitic aortitis: 1, Fluoroscopic evidence of aortic dilatation; 2, increased retromanubrial dullness; 3, history of circulatory embarrassment; 4, tympanitic, bell-like tambour accentuation of aortic second sound; 5, progressive cardiac failure; 6, substernal pain; 7, paroxysmal dyspnea.

The Kahn serologic test was positive in 92% of the series. The incidence of positive serology findings was practically the same in each group.

The average age for the entire group was 51 years. Seventy-one per cent were between the ages of 40 and 60. There were 154 males and 56 females. The ratio of males to females was: 2 to 1 in the group of uncomplicated aortitis; 3 to 1 in the group of aortitis with insufficiency; and 4.5 to 1 in the group of aneurysms.

The ratio of white patients to colored patients admitted to this hospital during the period covered by this study was approximately 47 to 1. In this series of cardiovascular lues, there were 196 white and 14 colored patients, a ratio of 14 to 1, or approximately 3 times more negroes than would be expected from the general admission ratio in this locality.

Analysis of the occupations of these cases showed that there were 73 laborers who had done heavy work; 47 tradesmen; 29 office workers; 6 professional men; and 55 housewives.

The probable duration of the syphilitic infection prior to diagnosis was ascertained in 170 cases. This was found to be more than 15 years in 90%.

Regarding treatment previous to diagnosis, 79% had had no antiluetic therapy; 17% had received poor treatment according to modern standards; and 4% had received only fair therapy. No case had received ideal or even good early antiluetic therapy. These findings are in accordance with those of the Coöperative Group for Study of Syphilis and recently published by Cole[3] and emphasize the value of early antisyphilitic treatment in preventing cardiovascular damage.

The blood pressure was found to be low or within normal limits in 138 cases. The systolic reading was between 145 and 200 mm. Hg in 63 cases, and above 200 in 9 cases. Care was exercised in making the diagnosis of uncomplicated syphilitic aortitis in the presence of high blood pressure.

The frequency of occurrence of neurosyphilis in cardiovascular syphilis is given by Riven and Feigenbaum[12] as 10% and by White[13] as 16 to 20%. In our series of cases there was some abnormality of the pupils in 23%. Spinal fluid examination was done on 96 cases. Some patients presented definite clinical evidence of luetic central nervous system involvement, but because of age or their general condition, a spinal puncture was not done. A total of 65 patients was found to have either clinical or serologic evidence of central nervous system syphilis. This was 31% of the total group studied. It is interesting that Burnett and Rymer[2] in a recent study of 215 cases of neurosyphilis report the occurrence of cardiovascular involvement in 33%.

In this series there were 34 deaths in the hospital, and postmortem examinations were performed on 21. Seven deaths were found to be due primarily to ruptured aneurysms, and 9 to aortic insufficiency with heart failure. There were 2 deaths in the group of simple aortitis, 1 of coronary occlusion, and 1 due to heart block together with cirrhosis of the liver. In the remaining 3 cases, the primary cause of death was not considered related to the cardiovascular system.

The extent of the thoracic aortic involvement is shown in Table 2.

TABLE 2.—EXTENT OF THORACIC AORTIC INVOLVEMENT.

Clinical type.	Aortitis uncomplicated.	Aortitis with insufficiency.	Aortitis with aneurysm.	Total.
Number of cases	83	66	61	210
Ascending arch	79 (95%)	66 (100%)	50 (82%)	195 (93%)
Horizontal	19 (23%)	20 (30%)	39 (64%)	78 (36%)
Descending	7 (8%)	5 (8%)	14 (23%)	26 (12%)

There was evidence of involvement of the ascending part of the aorta in 93% of the entire series of cases; 36% showed involvement of the horizontal part, and 12% of the descending aorta. A number of cases had involvement of more than one portion. The group of aortitis with aneurysm had almost 3 times as frequent involvement of the horizontal and descending portions of the aorta as the other two groups. This was found to be a very important characteristic, as in these locations there frequently was produced the so-called "silent" aneurysm with very few positive findings on physical examination.

Symptomatology. Table 3 shows the incidence of cardiovascular symptoms and also the general physical status of these patients on admission.

TABLE 3.—SYMPTOMS AND GENERAL CONDITION.

Type.	Aortitis uncomplicated.	Aortitis with insufficiency.	Aortitis with aneurysm.	Total.
Number of cases	83	66	61	210
Chief complaint referable to cardiovasc. system	12 (14%)	39 (59%)	32 (52%)	83 (39%)
Second. symptoms referable to cardiovasc. syst.	26	15	17	58 (28%)
No cardiovasc. symptoms	45 (54%)	12 (18%)	12 (20%)	69 (33%)
Able to work	79 (95%)	35 (53%)	32 (52%)	146 (70%)
Not able to work due to cardiovasc. symptoms	4	31	29	64 (30%)

The occult nature of cardiovascular syphilis is well illustrated by the finding that in the group of uncomplicated aortitis 54% had no symptoms at all which were referable to their cardiovascular system. Only 14% of this group came to the hospital because of chest symptoms and 32% had symptoms which were elicited in a careful history.

As might be expected, the incidence of symptoms was greater in the group of aortitis with insufficiency. The majority of these presented themselves in the medical clinic complaining of "heart trouble." The chief complaint of 59% of this group was referable to their cardiovascular system, and an additional 23% had secondary symptoms of such a nature. However, we wish to point out that even in this group having definite aortic regurgitation 18% had no cardiovascular symptoms. Some of these were found to have considerable cardiac enlargement and yet were entirely symptom-free.

In the group of aortitis with aneurysm only 52% came to the hospital because of chest symptoms, and 20% were entirely symptom-free.

In the entire series of cases studied only 39% presented a cardiovascular chief complaint, an additional 28% had symptoms which were elicited on careful history-taking, but 33% had no symptom referable to their cardiovascular system. In this one-third, the disease was entirely occult as far as warning signals were concerned and the patients were unaware that they had any heart trouble.

In the group of uncomplicated aortitis only 5% were unable to work due to their chest symptoms; and even in the entire series studied only 30% were incapacitated by their cardiovascular symptoms at the time of diagnosis.

Dyspnea and pain were the most frequent symptoms noted (Table 4).

TABLE 4.—SYMPTOMS OF DYSPNEA AND CHEST PAIN.

Type.	Uncomplicated aortitis.	Aortitis with insufficiency.	Aortitis with aneurysm.
Number of cases	83	66	61
Dyspnea on exertion	29 (35%)	55 (83%)	43 (70%)
Paroxysmal dyspnea	9	27 (41%)	22 (36%)
Pain.			
Definite substernal pain	24 (28%)	24 (36%)	30 (49%)
Angina-like attacks	9 (10%)	11	5
Sense of constriction or oppression in chest	6	12 (18%)	17 (23%)
Neuralgia of chest wall	2	1	16 (26%)
No chest pain	51 (61%)	28 (43%)	18 (30%)

In the group of uncomplicated aortitis only 35% gave a history of dyspnea on exertion. Only 28% said that they had had substernal pain, and 10% of these consisted of anginal-like attacks; 61% of this group had no chest pain or discomfort.

The incidence of symptoms was found to be considerably increased in the presence of insufficiency or aneurysm. Dyspnea was most frequent in the group of aortitis with insufficiency where it was present in 83%. Definite substernal pain occurred in 36% of this group and there was a sense of constriction or oppression in the chest in 18%. Of this group with insufficiency, 43% had no chest pain.

Definite substernal pain was found most frequently in the group of aneurysms where it occurred in 49%; 23% of this group had a sense of constriction or oppression in the chest. However, even in this group of aneurysm 30% had no chest pain or discomfort whatsoever, and 30% had no dyspnea on exertion.

The subjective sensation of palpitation was noted in 40%, being about equally distributed among each group. Cough occurred in 32% of the entire series but was most frequent in the group of aneurysm, where 78% had, or stated that they had been troubled by a prolonged cough. Hoarseness was rare, except in the group of aneurysm where it occurred in 44%. Difficulty in swallowing was noted in 13% of cases of aneurysm. There was found to be involvement of the horizontal portion of the aorta in 70% of the cases of aneurysm with cough and in practically all of those with hoarseness or difficulty in swallowing.

The duration of the cardiovascular symptoms for the entire series is shown in Table 5.

TABLE 5.—DURATION OF SYMPTOMS.

Less than 3 months	6
3 to 7 months	29
7 months to 1 year	43
1 to 2 years	49
2 to 4 years	10
More than 4 years	4
Total number with symptoms	141

Symptoms were of less than one year's duration in 55%, and less than 2 years' duration in 90%.

It is of interest to note that of the 83 cases that came to the hospital with a chief complaint referable to their cardiovascular system, 86% were found already to have either aortic insufficiency or aneurysm. And, furthermore, of the total number of cases having any cardiovascular symptoms (141) 73% were found already to have one of these major structural complications. Considering the poor prognosis in both of these conditions, it is obvious that treatment is indicated long before the appearance of symptoms, if the diagnosis can be made during the asymptomatic period.

Clinical Findings. The occurrence of the various findings on physical examination in the different groups is tabulated in Table 6.

The most frequent physical sign of aortitis was found to be a change in the quality of the second sound in the aortic area. This was found to be "tambour" in the majority of instances, sometimes merely accentuated. An abnormal second sound was present in

TABLE 6.—SUMMARY OF PHYSICAL SIGNS.

	Aortitis uncomplicated, 83.	Aortitis with insufficiency, 66.	Aortitis with aneurysm, 61.
I *Signs of Aortitis.*			
"Tambour" or changed A's	60 (72%)	..	32 (52%)
Systolic murmur at aortic area	42 (51%)	..	30 (50%)
None	18 (22%)	..	22 (36%)
II. *Signs of Aortic Insufficiency.*			
Marked carotid pulsation	7	48	22
Diastolic murmur at base	7	60	25
Abnormal pulse pressure	21	58	14
Cardiac enlargement (20% or more by Roentgen ray)	8 (9%)	53	20 (32%)
None	50	0	20
III. *Signs of Aneurysm.*			
Visible tumor or marked area of increased dullness at base	0	2	32 (52%)
Tracheal tug	0	6	22 (36%)
Paralysis of vocal cords	2	1	14 (23%)
Abnormal pupils (total, 48; 23%)	20	12	16
Difference of blood pressure of more than 10 mm. Hg in 2 arms	11	12	24 (40%)
None	54	35	11 (18%)

72% of the cases of uncomplicated aortitis and 52% of those with aneurysm. A systolic murmur at the aortic area was the next most common finding, being present in 51% of the simple aortitis group and 50% of those with aneurysm. There were found to be no physical signs of aortitis in 22% of the uncomplicated group and 36% of the aneurysm group. There was definitely roentgenologic evidence of cardiac enlargement in only 9% of the simple aortitis group although all had demonstrable aortic dilatation. Only 32% of the group with aneurysm were found to have cardiac enlargement.

The most frequent physical sign in the group of aneurysms was a visible tumescence or a marked area of increased dullness at the base. This occurred in 52% of this group. A tracheal tug was found in 36% of the cases with aneurysm and paralysis of a vocal cord was present in 23%. A difference in blood pressure in the two arms of more than 10 mm. Hg was obtained in 40% of the cases with aneurysm. It is important to note than 18% of the cases of aneurysm presented no physical signs of heart disease even on careful examination. All of these were found to have involvement of the horizontal or descending portions of the aorta.

Electrocardiographic study was made in 81 cases. The majority of these were from the group with aortic valve insufficiency or complained of angina-like pain. The most frequent findings were an abnormal left axis deviation, being present in 41 cases. Arrhythmia was found in 17, and 4 cases presented evidence of conductive block. There was an abnormal *QRS* complex or *S–T* interval in

14 cases. Normal electrocardiographic tracings were reported in 13 of the 81 cases studied. We have not been impressed by the usefulness of electrocardiogram study in early diagnosis of aortitis.

Summary. 1. An analysis of 210 cases of syphilitic cardiovascular disease is presented. These consisted of 83 cases of uncomplicated aortitis, 66 cases of aortitis with insufficiency and 61 cases of aneurysm.

2. In the group of uncomplicated aortitis 54% of the cases were found to have no symptoms referable to their cardiovascular system. Only 14% of this group came to the hospital because of heart trouble. Even on careful physical examination no clinical signs of aortitis were found in 22% of this group.

3. In the group of aortitis with insufficiency 18% were asymptomatic so far as the cardiovascular system is concerned.

4. In the group of aneurysm 20% had no symptoms suggesting mediastinal lesions and furthermore 18% presented no abnormal physical findings, *i. e.*, the process was entirely occult clinically.

5. In the entire series studied the disease was found to be occult symptomatically in one-third of the cases.

Conclusions. In view of these findings the diagnosis of these occult manifestations at an early stage is obviously difficult. In every syphilitic patient during the period of latency the cardiovascular system must be suspected and particular significance attached to the minor physical findings in this group. When these are present, particularly changes in the aortic second sound and a soft systolic murmur at the aortic area, a strong suspicion must arise that early occult cardiovascular disease exists. Such findings, therefore, require complete investigation, which should include a careful fluoroscopic study together with orthodiagraphic or teleoroentgenographic measurements of the heart and of the aortic caliber.

When symptoms referable to cardiac disease occur in a known syphilitic, most of these will already be found to have developed either aortic insufficiency or marked increase in aortic caliber, which may be regarded as aneurysmal dilatation.

In the series studied, dyspnea occurred far more commonly with aortic insufficiency whereas pain was a prominent symptom in both early and late aneurysm. In the aneurysmal group it is important to emphasize that marked increase in caliber cannot be excluded by normal cardiac physical findings particularly in cases where the aortic ring itself is not involved. The occasional freedom from symptoms even in large dilatations and the existence of marked symptoms in small aneurysms constitutes a diagnostic paradox of great interest. The size of the aneurysm is not nearly so marked a factor in the production of symptoms as its location.

The frequency with which asymptomatic patients are found upon careful physical examination to have definite aortitis, and not infrequently even aneurysm, emphasizes the importance of a careful roentgenologic study of both heart and aorta of all cases of syphilis in their period of latency.

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*THE CARDIOVASCULAR COMPLICATIONS OF HYPERTHYROIDISM.**

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SINCE the original description of exophthalmic goiter by Parry,[2] it has been recognized that symptoms and signs referable to the cardiovascular system occupy a prominent place in the clinical picture of hyperthyroidism. The present communication summarizes the results of an analysis of the cardiovascular complications in a series of 1000 consecutive cases of thyrotoxicosis with particular reference to the incidence of organic heart disease, congestive heart failure and important disturbances of cardiac rhythm.

Material and Results. The age of the 1000 patients ranged from 3 to 81 years; 237 were males and 763 were females. Four hundred eighty-eight were classified as having diffuse goiter, 353 nodular or adenomatous goiter, 119 combined diffuse and nodular goiter, and 28 colloid goiter. Surgical treatment was carried out in 988 patients, while in 12 the severity of the thyrotoxicosis or the presence of some serious complication prevented active treatment or made Roentgen therapy the procedure of choice.

Of the 1000 patients, 173 presented clinical or electrocardiographic evidence of organic heart disease, while 32 additional individuals had enlargement of the heart by roentgenologic examination but presented no other signs of organic heart disease (Table 1). Although it is possible that some of the latter may have had pathologic myocardial changes, it is believed that in the great majority the enlargement was due to simple dilatation incident to the thyrotoxicosis. Hearts of normal size showing no signs of organic heart disease were found in 795; arterial hypertension was present in 43 of these.

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* Read before the American Clinical and Climatological Association, Baltimore, Md., October 11, 1937.

Important disturbances of cardiac rhythm were observed in a little over 20% of the 1000 patients (Table 2). Auricular fibrillation occurred in 207 individuals; in 96 the arrhythmia was recorded before operation either in its continuous form or in paroxysms of long or short duration, while in 111 it developed for the first time as a postoperative complication. Approximately one-half of the patients with auricular fibrillation presented evidence of organic heart disease. In 94 individuals, however, the arrhythmia occurred in the absence of organic heart disease, while in 9 additional patients the only abnormality detected consisted of slight enlargement of the heart by roentgenologic examination. Auricular flutter occurred in 2 patients, auricular paroxysmal tachycardia in 5, and ventricular paroxysmal tachycardia in 2. Premature beats also were encountered; but their incidence did not seem to be appreciably greater than in the general run of patients seeking medical advice for conditions other than thyrotoxicosis.

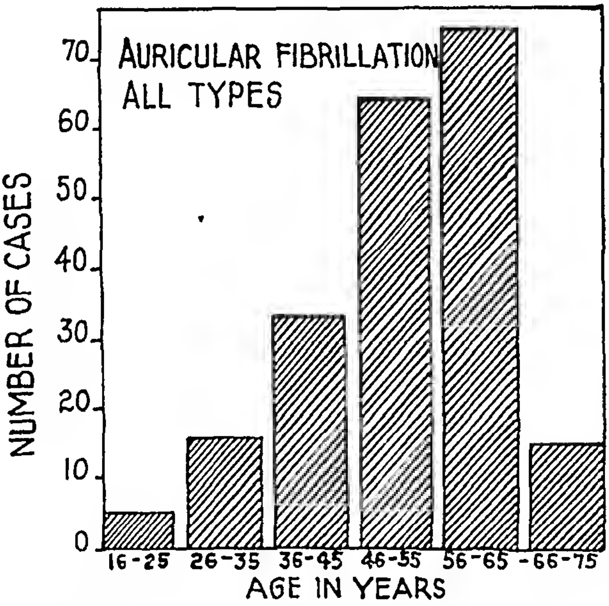

Fig. 1.—The age incidence of auricular fibrillation in hyperthyroidism.

The case histories of the patients with auricular fibrillation were analyzed with reference to the effect of age, duration of hyperthyroidism, type of goiter and the degree of elevation of the basal metabolic rate upon the incidence of the arrhythmia. All three types of auricular fibrillation, namely the continuous form, the paroxysmal form present before operation, and auricular fibrillation which develops for the first time as a postoperative complication, were more common in patients over 45 years than in younger individuals. When the three forms were considered together, approximately 75% of all cases were found to have occurred in persons beyond the age of 45 (Fig. 1). There was no apparent

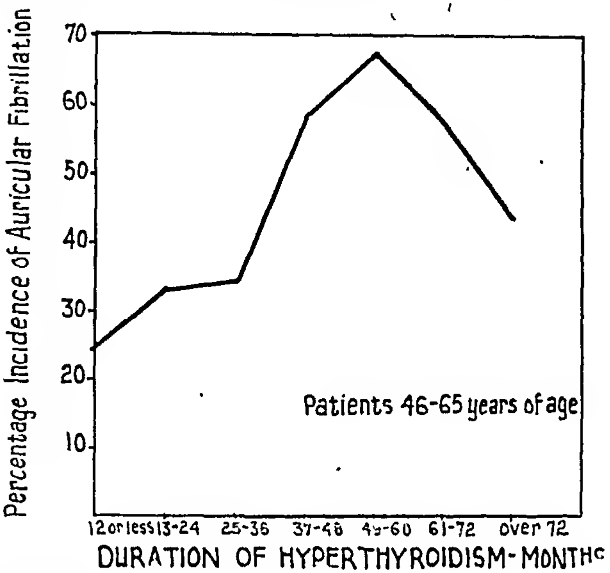

FIG. 2.—The effect of the duration of hyperthyroidism on the incidence of auricular fibrillation.

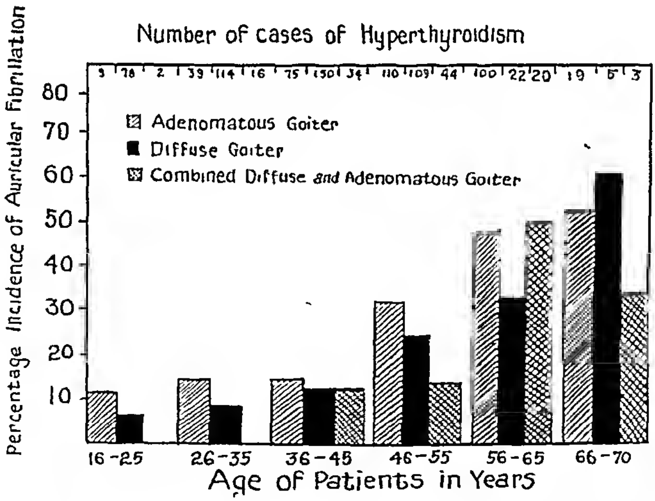

FIG. 3.—The effect of the type of goiter on the incidence of auricular fibrillation.

relationship between the duration of the hyperthyroidism and the incidence of auricular fibrillation when all patients with the arrhythmia were considered together. When individuals of the age group with the greatest incidence of auricular fibrillation (46 to 65 years) were considered separately, however, the arrhythmia occurred much more frequently in those who had had thyrotoxicosis for 3 or more years than in those who had had symptoms for a shorter period (Fig. 2). In every age group up to 65 years, the percentage incidence of auricular fibrillation was greater in patients with adenomatous goiter than in those with diffuse goiter (Fig. 3). Auricular fibrillation occurred in 31% of 353 patients who had adenomatous goiter, in 14% of 488 individuals with diffuse goiter, and in 18% of 119 patients with combined diffuse and adenomatous goiter. No rela-

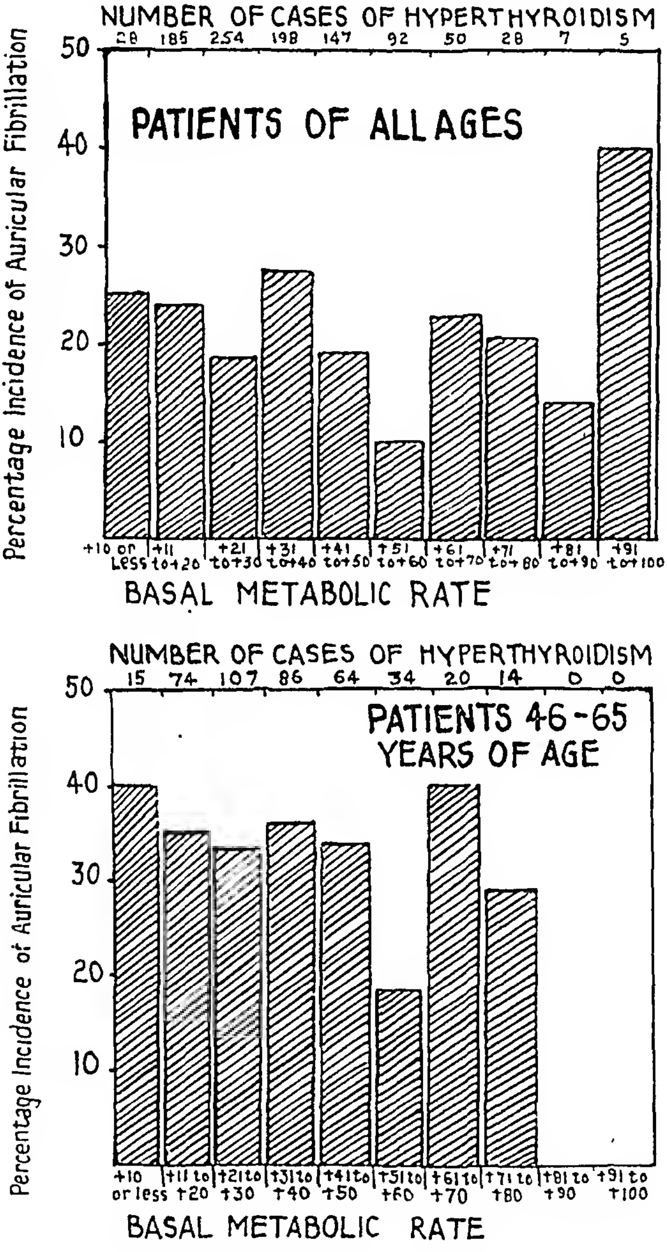

Fig. 4.—The absence of relationship between the basal metabolic rate and the incidence of auricular fibrillation.

tionship was demonstrable between the degree of elevation of the basal metabolic rate and the incidence of auricular fibrillation whether one considered all patients together or limited the analysis to the age group with the greatest incidence of the arrhythmia (46 to 65 years) (Fig. 4).

The course of the three types of auricular fibrillation is presented in Table 3. Normal sinus rhythm was reëstablished spontaneously within 10 days after operation in one-third of the patients with the continuous form of the arrhythmia. Quinidine sulphate was administered after the tenth postoperative day to one-half of the remaining patients in the group, and in 60% of these reversion to sinus rhythm occurred. Of the 27 patients who had paroxysmal auricular fibrillation before operation, 15 experienced a recurrence of the arrhythmia after operation, and in all of these except 2 who died, normal rhythm was reëstablished within 5 days. In the group in which auricular fibrillation developed for the first time as a postoperative complication, spontaneous reversion to sinus rhythm occurred in all patients who survived as well as in 4 of the 10 who died.

Congestive heart failure was present in 44 of the 1000 patients (Tables 1 and 2). Approximately two-thirds of these had auricular fibrillation, and all but two presented evidence of organic heart disease. The two exceptions had auricular fibrillation and showed limited enlargement of the heart by roentgenologic examination

TABLE 1.—ORGANIC HEART DISEASE IN 1000 CONSECUTIVE CASES OF HYPERTHYROIDISM.

Type of heart disease.	No. of cases.	With auricular fibrillation.	With congestive failure.
Arteriosclerotic	85	57	18
Hypertensive	64	35	17
Rheumatic	22	12	7
Luetic aortitis	1	0	0
Congenital cardiac anomaly	1	0	0
Enlargement of heart without other evidence of organic heart disease	32	9	2
No cardiac enlargement—no evidence of organic heart disease	795	94	0
Totals	1000	207	44

TABLE 2.—DISTURBANCES OF CARDIAC PHYSIOLOGY IN 1000 CONSECUTIVE CASES OF HYPERTHYROIDISM.

Type of disturbance.	No. of cases.	
Auricular fibrillation	207	
With organic heart disease		104
Without organic heart disease		103
Auricular flutter	2	
Auricular paroxysmal tachycardia	5	
Ventricular paroxysmal tachycardia	2	
Congestive heart failure	44	
With auricular fibrillation		29
With normal rhythm		15
Angina pectoris	5	
Cardiac asthma	3	

but this was considered to be due to dilatation rather than to myocardial disease.

Five of the 1000 patients had angina pectoris and 3 had cardiac asthma.

TABLE 3.—THE COURSE OF AURICULAR FIBRILLATION IN HYPERTHYROIDISM.

Type of auricular fibrillation	No. of cases.
Continuous	69
No operation	9
Patient died after operation	6
Spontaneous reversion to sinus rhythm after operation	21
Quinidine sulphate administered after operation	20
Auricular fibrillation persisted	8
Reversion to sinus rhythm	12
Quinidine sulphate not given—auricular fibrillation persisted	13
Paroxysmal before operation	27
Auricular fibrillation recurred after operation	15
Spontaneous reversion to sinus rhythm	13
Auricular fibrillation persisted until death	2
No recurrence of auricular fibrillation after operation	
Postoperative	111
Patient died	10
Postoperative auricular fibrillation persisted until death	6
Spontaneous reversion to sinus rhythm before death	4
Patient lived	
Spontaneous reversion to sinus rhythm	101

The postoperative mortality was considerably greater in patients who had auricular fibrillation either before or after operation than it was in individuals with normal cardiac rhythm (Table 4). This was true whether or not the patient with auricular fibrillation presented evidence of organic heart disease. Factors which appeared to influence postoperative mortality most importantly, however, were the severity of the thyrotoxicosis, the age of the patient and the intensity of the postoperative reaction. Of the 18 patients who had auricular fibrillation either before or after operation and who died after operation, only 6 were less than 55 years of age. Evidence of organic heart disease was present in one-half of the 18 patients but in only 5 was congestive heart failure a contributory cause of death. Of the 11 patients who had no disturbance of cardiac rhythm and who died after operation, 6 had organic heart disease but in only one was congestive heart failure a contributory cause of death.

TABLE 4.—MORTALITY STATISTICS.

	No. of cases.	Deaths after operation.	Mortality (%).
Total series—consecutive cases subjected to operation	1606	32	2.0
Adenomatous goiter without hyperthyroidism	618	3	0.5
Hyperthyroidism	988*	29	2.9
With regular rhythm	790	11	1.4
With auricular fibrillation	198	18	9.1
Auricular fibrillation present before operation	87	8	9.2
Postoperative auricular fibrillation only	111	10	9.0

* No operation performed in 12 of the 1000 cases of hyperthyroidism studied.

Discussion. Organic heart disease constitutes one of the most important complications of hyperthyroidism. Usually the cardiac condition has caused little or no trouble prior to the onset of thyrotoxicosis, but the increased load on the heart during hyperthyroidism frequently results in the development of significant cardiovascular symptoms and signs. Chief among these are auricular fibrillation and congestive heart failure while auricular flutter, paroxysmal tachycardia, angina pectoris and cardiac asthma occur at times.

Auricular fibrillation occurs either in its continuous form or in paroxysms of variable duration in about 10% of all patients with hyperthyroidism. In another group of about the same numerical size, the arrhythmia develops as a temporary disturbance within 2 or 3 days after thyroidectomy. Although auricular fibrillation occurs at times in young individuals with normal hearts, approximately one-half of all patients have organic heart disease. Seventy-five per cent of the patients are more than 45 years of age and, it is evident, therefore, that myocardial or coronary artery changes constitute an important predisposing factor even though these changes may not be detectable by clinical means alone. The duration of the thyrotoxicosis and the type of goiter also influence the incidence of auricular fibrillation while the degree of elevation of the basal metabolic rate has no effect. From clinical observation alone, however, one obtains an impression that the arrhythmia is more common in patients who present a general picture of severe hyperthyroidism.

The more frequent occurrence of auricular fibrillation in individuals with adenomatous goiter than in those with diffuse goiter probably is due in large part to the longer average duration of thyrotoxicosis in the former group but another important factor may be present. There is considerable evidence that many patients with adenomatous goiter have previously experienced prolonged or repeated periods of low-grade unrecognized hyperthyroidism. Such subclinical thyrotoxicosis may favor the gradual development of myocardial damage and thus predispose to the occurrence of auricular fibrillation.

The factors which predispose to the development of auricular fibrillation as a postoperative complication are the same as those which govern the occurrence of the arrhythmia before operation.[1] In postoperative auricular fibrillation, however, an additional stimulus connected with the operation or the early postoperative course is necessary to initiate the arrhythmia. Segal and Means[3] demonstrated that the basal metabolic rate is increased to a variable but usually considerable degree during the first few days after subtotal thyroidectomy in patients with hyperthyroidism. The rise, they believe, is the result principally of fever and emotional disturbance. It seems probable that this rapid increase in the metabolic rate and the consequent increased load upon the heart are the essential factors responsible for the initiation of auricular fibrillation, and that the same factors may also control the duration of the arrhythmia. It must be emphasized, however, that the abnormal rhythm may occur in individuals in whom the postoperative reaction and elevation in temperature are of mild degree.

Congestive myocardial failure, generally of slight or moderate degree but occasionally severe, occurs in approximately 4% of all patients with hyperthyroidism. Very active thyrotoxicosis usually is present but mild hyperthyroidism of long duration results at times in the development of advanced failure. The two most important factors responsible for congestive failure are the presence of organic heart disease and the occurrence of uncontrolled auricular fibrillation. Auricular fibrillation is present in approximately two-thirds of all patients in whom failure develops, and the great majority of these either present evidence of organic heart disease or are of such an age that the possibility of changes in the coronary arteries cannot be excluded. In unusual instances, however, congestive failure appears to be the direct result of uncontrolled auricular fibrillation in a young person who presents no evidence of organic heart disease. On the other hand, organic heart disease is almost always present in individuals in whom thyrotoxicosis is complicated by myocardial failure with normal cardiac rhythm.

The greater postoperative mortality in patients who have auricular fibrillation either before or after operation cannot be interpreted as evidence that the arrhythmia *per se* greatly increases the operative risk. Congestive heart failure was a contributory cause of death in less than one-third of the fatal cases in which auricular fibrillation was present. Moreover, in 4 of the 10 fatal cases in which the arrhythmia developed as a postoperative complication, normal rhythm was reëstablished spontaneously before death. Such spontaneous reversion to sinus rhythm does not occur in a failing heart. The statistics simply indicate, therefore, that auricular fibrillation is more common in patients in whom, because of age, the general condition of the individual and the severity of the hyperthyroidism, postoperative mortality is greater. Emphasis must be placed not upon the danger of auricular fibrillation but upon the necessity for thorough, unhurried pre-operative care in all elderly patients, in all individuals with severe hyperthyroidism, and in all with auricular fibrillation.

Summary and Conclusions. 1. A study has been made of the cardiovascular complications in 1000 consecutive cases of hyperthyroidism.

2. Clinical or electrocardiographic evidence of organic heart disease were present in 173 patients; 32 others had enlargement of the heart by roentgenologic examination but no other signs of organic heart disease.

3. Auricular fibrillation occurred in 207 patients. In 96 of these, the arrhythmia was present before operation either in its continuous

form or in paroxysms of variable duration, while in 111 it developed for the first time as a postoperative complication.

4. The factors which influenced the incidence of auricular fibrillation most importantly were the presence of organic heart disease, the age of the patient, the duration of the hyperthyroidism and the type of goiter. The degree of elevation of the basal metabolic rate had no effect.

5. Normal sinus rhythm was reëstablished spontaneously in one-third of the patients with the continuous form of auricular fibrillation. Quinidine sulphate was administered to one-half of the remaining patients in this group, and in 60% of these reversion to sinus rhythm occurred.

6. Congestive heart failure was present in 44 patients. The two most important factors responsible for this complication were organic heart disease and uncontrolled auricular fibrillation.

7. The postoperative mortality was considerably greater in patients who had auricular fibrillation either before or after operation than it was in individuals with normal cardiac rhythm.

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BOOK REVIEWS AND NOTICES

General Hygiene and Preventive Medicine. A Text-book for College Students, Medical Students, Nurses, Public Health Workers and Social Workers. By John Weinzirl, M.S., Ph.D., Dr. P.H., Late Professor of Bacteriology and Director of the Alice McDermott Foundation of the University of Washington; Technical Adviser on Public Health to the Washington State Planning Council, etc. Edited by Adolph Weinzirl, B.S., M.D., C.P.H., Health Officer, Portland, Oregon; Clinical Professor of Public Health, University of Oregon Medical School, etc. Pp. 424. Philadelphia: Lea & Febiger, 1937. Price, $4.00.

This text is intended primarily for college students in the upper division, medical students, nurses, and teachers in training. It is a formidable task to attempt to meet the needs of four such diverse groups. Hope that some measure of success may attend this effort is derived from the fact that the subject matter is approached from a new angle. Certainly in no field of textbook writing is originality in presentation more sorely needed.

The new angle of approach is characterized by presentation of the subject matter categorically classified as a disease or as a method of control. This idea has been pursued to the practical exclusion of every other consideration. The peculiarities in subject arrangement, of definition and of coördination which result will impress most readers as being unusual in the extreme. Thirty-two methods of control are named and discussed under as many chapter headings. Under each is given a brief account of three or four diseases which are thought to be illustrative of its application. The following are typical; under "Bacterination as a Method of Controlling Disease" are typhoid fever, furunculosis, and Rocky Mountain spotted fever; under "Serumation as a Method of Controlling Disease," tetanus, hog cholera, and snake poisoning; under "The Use of Specific Surgery as a Method of Controlling Disease," arthritis, pyorrhea, hyperthyroidism, and cancer; under "Isolation as a Method of Controlling Disease," influenza, poliomyelitis, encephalitis; under "Epidemiology as a Method of Controlling Disease," septic sore throat, foot-and-mouth disease, and gonorrhea; under "The Control of Humidity as a Method of Controlling Disease," inefficiency and nervousness; under "The Control of Clothing as Method of Controlling a Disease," common cold and pneumonia; under "Public Health Organization as a Method of Controlling Disease," bubonic plague, Asiatic cholera, and ankylostomiasis; under "The Control of the School Group as a Method of Controlling Disease," human tuberculosis, colloid goiter, dental caries. Thus "epidemiology" and "public health organization are considered to be methods of control coördinate with vaccination against smallpox. The time-honored groupings of diseases which may be controlled by purification of water supplies and by the sanitary supervision of milk production and distribution receive no special attention. Inefficiency, frostbite and obesity are treated as diseases in the same manner as is plague, measles and scarlet fever.

Each "disease" is discussed under five section headings, history, disease, epidemiology, prophylaxis and treatment. Adherence to this division is rigidly maintained, whether the subject under discussion be leprosy or yellow fever, or whether it be insomnia or senility.

Upon reviewing these arrangements and presentation of subject matter, one cannot help but feel that the approach from this new angle has not been productive of increased clarity of thought. On the contrary, the attempt to classify categorically according to a rigid plan with ruthless consistency has forced the authors into many awkward positions, into repetitious phraseology, into connotations not generally acceptable, and into dangers of misinterpretation. The basis of the classification which has been used is at variance with the very fundamentals of the subject matter. Hygiene does not deal with disease alone but with deviation from good health and social well-being of various magnitudes, which do not necessarily fall within the generally accepted definition of disease. Again the prevention and amelioration of diseases, abnormal states, and social problems is almost without exception an intricate matter for which no single method of control suffices, but for which a combination of several methods is required, varying with the circumstances. To discuss a disease as a subheading under a single method of control is to run the very definite risk of giving the student the impression that this is the only or at least the most important method. In like manner to classify all human ailments and social problems under methods of control is to run the risk of leaving the net impression that all are amenable to control—an impression which is violently at variance with the known facts.

If the reader can disregard these considerations and concentrate attention upon the text itself, a mass of useful material will be found incorporated. The actual discussion of diseases, disturbed functional states, and social problems is in general accurate to a degree greater than is usual in this field of textbook writing. There is a charming simplicity and clearness of style. There is a freedom from complicated statement, technical detail, and reference to original sources which will delight the soul of many undergraduates. The more earnest seekers after knowledge, and with these we would identify most students of medicine, who want to be informed more exactly about techniques and procedure, who want to understand disease, disturbed function and maladjustment as a reaction between the human organism and its physical and social environment, and who want to consider judicially the possibilities of prevention from the point of view of the individual, the physician, the health officer, and the community, will be left unsatisfied. K. M.

THE LABORATORY DIAGNOSIS OF SYPHILIS. The Theory, Technic, and Clinical Interpretation of the Wassermann and Flocculation Tests With Serum and Spinal Fluid. By HARRY EAGLE, M.D., Passed Assistant Surgeon, U. S. Public Health Service, Washington, D. C.; Lecturer in Medicine, Johns Hopkins University Medical School, etc. With a Foreword by J. EARLE MOORE, M.D., Associate in Medicine, Johns Hopkins University; Physician in Charge, Syphilis Division of the Medical Clinic, and Assistant Visiting Physician, Johns Hopkins Hospital. Pp. 440; 27 illustrations and 53 tables. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

THIS book, by an able serologist, is moderate in size and price, erudite and yet understandable in content, and is a genuine contribution to medical literature. The serology is distinctly that of the author—there are some 25 or more of his titles in the bibliography as against half a dozen or so for other distinguished contributors to serologic problems and technique. This however is by no means a crucial matter, for serology has long been personal, and the author is unquestionably a master. The clinical interpretations, well woven into the fabric of the book, are under the egis of the Johns Hopkins group, headed by Moore. It is inevitable that work from one of the great syphilologic centers of the world should command respectful hearing and admiration for its high and distinctive quality.

An introduction, which brings out the essential unity and the chronologic sequence of events in the development of diagnostic serum tests for syphilis, is followed by Part I, on the Wassermann reaction, with a full consideration of practical technical detail and an illuminating discussion of the physics and physical chemistry of serum reactions. No one who has to do with the interpretation of serologic tests in a clinic can be other than enlightened by the clarity of this discussion and by such important critical summarizations as that on page 131, *et seq.* The presentation of this section must be invaluable to anyone called upon to supervise a laboratory or a group of technicians or, from the clinical side, to intervene (meddle!) in the problem of interpreting conflicting results. Eagle describes three adequate Wassermann techniques, and proceeds to Part II, which is an equally illuminating discussion of flocculation tests. The essential unity of complement fixation and precipitation procedures is insistently and, to the Reviewer, quite clearly brought out. The analysis of factors affecting sensitivity and specificity in the increasingly popular flocculation procedures, is timely, and of high critical value. Seven representative flocculation techniques in current use are described, including the 4 which have given America distinction in this field. Part III is an invaluable section on the examination of the spinal fluid. The author rates the flocculation test on the spinal fluid as distinctly less sensitive than the Wassermann procedure. Part IV deals with the esoteric tests for syphilis, which have as yet little if any practical usefulness. The luetin test receives short shrift.

In Part V, on the clinical evaluation of the serologic report, lucid restatement and interpretation of facts and material familiar as yet only to clinical experts make this book a useful desk reference for most practising diagnosticians. Here is available a full discussion of the combined serologic and clinical significance of treatment response, provocative effects, Wassermann (reagin) fastness, serologic relapse and spinal fluid changes under treatment. To those who have watched the progress of international serologic conferences and the efforts recently made in this country to put American serologic laboratories on a sound comparative and interpretative basis, the close of Eagle's book is a mine of interesting material. He converts the sometimes complex and occasionally equivocal or masked conclusions of the official reports into sharp percentage differences that lead up inevitably to one of the most significant paragraphs in the entire book: "It seems clear that a good technic does not, *per se*, insure the proper performance of a test. Every test for syphilis, however sensitive and however specific it may be under ideal conditions, is limited in actual performance by the capacities of the individual who carries it out. The gross inadequacy of the diagnostic test as now performed in many laboratories is only too apparent from Table LII . . . .

"But even more important than the combined refinement of the serologic procedures is a more critical attitude on the part of the individual laboratory to the calibre of its own performance. . . . . It is nevertheless to be hoped that those responsible for the organization of these first two American conferences will set up a permanent body whose function it will be to organize similar conferences, either because of new technics to be evaluated, or additional laboratories to be checked."

It is a pleasure to commend a work of this sort to the serious attention of all who must diagnose syphilis—and what physician, indeed, must not?

J. S.

CLINICAL REVIEWS OF THE PITTSBURGH DIAGNOSTIC CLINIC. Guideposts to Medical Diagnosis and Treatment. Eight Contributors. Edited by H. M. MARGOLIS, B.S., M.D., F.A.C.P. Pp. 552; 6 figures, 5 charts and 4 tables. New York: Paul B. Hoeber, Inc., 1937. Price, $5.50.

A SERIES of 45 articles, 35 of them by the Editor, dealing with the present status of our knowledge in a number of diseases in the domain of internal medicine. The topics have been selected chiefly with a view to their practical importance or to the recent development of new and important information, and include such conditions as the psychoneuroses, various endocrinopathies (e. g., pituitary disorders, goiter, Addison's disease, hyperparathyroidism, diabetes, protamine zinc insulin, obesity), focal infection, arthritis, coronary disease, hypertension, nephritis, the anemias, serum reactions, undulant fever, amebiasis, rectal bleeding, colitis, peptic ulcer and dental conditions. The articles are well written, concise, and reliable in their information. To each chapter are appended a number of references to the more important recent literature. The practitioner will find here much that is helpful and instructive. R. K.

TEXTBOOK OF GENERAL PHYSIOLOGY. By T. CUNLIFFE BARNES, D.Sc., Assistant Professor of Biology, Yale University. Pp. 554; 166 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.50, with washable cloth cover.

LABORATORY MANUAL OF GENERAL PHYSIOLOGY. By the same author and publisher, 1937. Pp. 116 (every other page blank, excepting Index); 9 illustrations. Price, $1.00, with washable paper cover.

SINCE there is no general agreement as to the boundaries of the all-inclusive subject of General Physiology, each author of a textbook in this field is free to select and to emphasize those topics which interest him most. Availing himself of this privilege, the present author in his larger volume has laid especial emphasis upon two subjects usually not very fully treated in similar works, namely, the physical and other properties of water, including 22 pages devoted to heavy water, and physical models of living systems. Other subjects treated with varying degrees of thoroughness are: diffusion, osmosis, and electrolytes; surface action in liquids; colloids; the nature of living matter; permeability; amœboid and ciliary movement; muscular contraction; animal behavior; nervous action; bioelectrical potentials; temperature characteristics; biological oxidations and respiratory pigments; general physiology of the heart; and chemical regulation by hormones.

A unique feature of the book is the character of some of its illustrations, in which vividness is gained by a touch of humor rarely found in textbooks. Many persons will question, however, whether clear thinking on the part of the student is promoted by regarding the slowest chemical reaction in a catenary series as analogous to a horse-drawn load of hay on a crowded thoroughfare, or the chloride shift in the blood as resembling the emergence from the red cells of a dog, labeled Cl, to take possession of a bone, labeled Na, when a larger dog, labeled CO_2, leaves the blood. Of particular value in the textbook is a bibliography of some 1600 titles, including many very recent ones. No reader who uses this part of the volume with diligence can fail to add to the breadth of his knowledge of General Physiology.

The Laboratory Manual, which is designed to accompany the textbook, is bound in flexible covers and contains blank pages for the student's notes. The experiments, derived from various sources acknowledged in the preface, illustrate a variety of topics, which, following the classification of the author, may be grouped under the general headings of animal behavior, physical and chemical principles, influence of external factors on the organism, and internal factors in the organism. M. J.

HEILKUNDE UND VOLKSTUM AUF BALI. By DR. MED. WOLFGANG WECK, ehem. Hoofd-Gouvernementsarzt in Niederländisch-Indien. Pp. 248; 27 illustrations. Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 19; Bound, Rm. 20.60.

THE East Indian island of Bali, like its western neighbor, Java, to which it physically belongs, is inhabited by a Javanese race, has a similar language and, like Java, is owned by the Dutch. Its religion, however, differs in that Hinduism and its widow-burning suttee is still practised, blended with Buddhism and a belief in Kalas, or evil spirits. It is this blend of religions and folk customs which gives a special interest to this authoritative presentation. Though the culture of Bali was declining before the Dutch arrived, their folklore remains rich, while their medicine, according to Dr. Weck, results from a combination of an autochthonous demonology with a mystic philosophy derived from Indo-Aryan newcomers during a millenium and a half.

Bali is fast becoming a favorite stop-off for globe trotters, world cruises and the like, so that this work by a former chief government physician of the West Indies who has spent many years studying his subject in native books and with native physicians is, indeed, timely. Not that it invites the tourist or superficial observer; rather is it a sober statement for ethnologists and medical historians of the medical theories and practices of an ancient but still isolated and primitive people. E. K.

RECENT ADVANCES IN PULMONARY TUBERCULOSIS. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital; Physician to Brompton Hospital for Consumption and Diseases of the Chest, etc. Pp. 320; 22 text illustrations and 48 plates. Third Edition. Philadelphia: P. Blakiston's Sons & Co., Inc., 1937. Price, $5.00.

A COMPACT work primarily intended for general practitioners and students. The author has tried to separate the real advances from those methods which have no scientific basis. The major portion of the book is devoted to treatment, though the newer aspects of diagnosis and especially immunity and infectivity are adequately covered. The sections dealing with hemoptysis and gold therapy are especially noteworthy. The author's literary style makes delightfully easy reading. Many illustrative radiographs are inserted at the end of the book. L. L.

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM. Anatomy, Physiology, Pathology, Experiments and Clinical Applications. By HUGO ROESLER, M.D., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, etc. Pp. 343; 199 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

THIS is probably the finest review of the present stage of our knowledge of cardiovascular roentgenography that has been published in English. While the volume is definitely clinical in its approach, the value of its material is enhanced by the anatomical, physiologic and pathologic data incorporated in the discussion of the various cardiovascular diseases. The excellent illustrations are of considerable assistance to the reader. We do not hesitate to recommend this volume as a textbook. It may also be used as a reference book as its bibliography is unusually complete. P. H.

THE PATIENT AND THE WEATHER. Volume IV, Part 2. *Organic Disease.* Hypo and Hyperthyroidism, Diabetes, The Blood Dyscrasias, Tuberculosis. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 729 (lithoprinted), 380 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937. Price, $11.00.

IN the preface of this voluminous work it is more than suggested that reviewers of these volumes who charge overemphasis of the meteriologic environment, are confining their readings to chapter headings. Attention continues to be directed toward the synthetic approach to medical problems, rather than to the analytical method so much employed in the laboratory and clinic.

Chapter I, The Cretin and the Hyperthyroid: The cretin, who is relatively inactive to the environment, appears to become more active upon the administration of thyroid substance. Thyrotoxic crises are prone to follow extreme meteorological changes. Hyperthyroidism and exophthalmic goiter are more frequent in the American Storm Track areas. In exophtalmic goiter there appeared to be a marked trend for deaths to follow polar crests. Chapter II, Diabetes: The ARS phase—anabolism, reduction and vascular constriction—tends toward a hyperglycemia and the production of intermediary acid bodies; the COD phase—catabolism, oxidation and dilatation of the vascular bed—tends toward an acidosis. In the terminal stage of diabetes, with impaired function of the myocardium, brain, kidneys and skin, there was response to very slight environmental changes. Chapters III and IV, The Blood Dyscrasias: These constitute approximately half the volume—actually 360 pages. Polar episodes were definitely followed by leukopenia and tropical ones by improvement and restoration. Roughly, patients may be grouped under three headings: 1, The very young who are particularly responsive to environmental changes and in whom, because of their youth, the cytopoietic components are particularly responsive and labile; 2, those slender, poorly buffered adults, with other evidence of instability; and the vegetatively stigmatized group, coming from families who show colitis, goiter, ulcer, migraine and arteriosclerosis, in whom the sex rhythm may be pronounced as in the granulopenia group; 3, The senile group with its oncoming vascular impairment, when the smaller vessels become less efficient. "The really great excitant, oxygen deficiency, is always lurking in the background; this is the common denominator which, registering on susceptible tissues, may bring about the multitude of clinical pictures." Chapter V, Tuberculosis: But little consideration is found here—no discussion of pertinent literature—but later, its comprehensive study will appear in a monograph in collaboration with the author's associates. However, there are some data pertaining to the various types of pulmonary tuberculosis, tuberculous meningitis and Potts' disease.

At the end of each chapter is found an abundant supporting bibliography. As with the preceding volumes, this, the most ponderous, will find its greatest use with the research worker and the specialist. It is hoped that the final volume of this monumental work will contain a glossary and an index.

N. Y.

CONDITION SATISFACTORY. A Physician's Report of His Own Illness. By DR. SÁNDOR PUDER. Translated from the German by HILDEGARD NAGEL. With a Foreword by FRIGYES KARINTHY. Pp. 201. New York: Alfred A. Knopf, 1937. Price, $2.00.

"THE author of this book, a practicing physician, was forced to undergo three successive operations. What he experienced—what he saw, felt and thought—during that dangerous and painful period forms the subject of this extraordinary book. A story of human pain, placed against a background of operating-rooms, laboratories, flashing instruments, and anaesthetic apparatus, only a physician could have produced so authentic a record of the 'psychic life' of a patient."

The above indicates the nature of this well translated, moving story. The author is a tuberculosis specialist of note who is now in charge of the tuberculosis ward of the National Social Insurance Institute of Hungary and is consulting physician in Koranyi's clinic.

E. K.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital, Boston. Pp. 219; 49 illustrations and 1 colored plate. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $2.00.

THIS sixth edition maintains the high standard of former editions. The only notable change is the inclusion of the use of protamine zinc insulin. This is not set apart in a separate chapter but is included as an integral part of the instruction regarding the balance and care of the diabetic. The manual continues to be probably the most valuable diabetic guides for both physician and patient. R. R.

CLINICAL PARASITOLOGY. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., COL. U. S. A (RETIRED), D.S.M., Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 733; 243 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

IN the introductory chapter are outlined and illustrated certain general considerations of parasitism and parasitic disease. The discussions of the various groups of organisms are arranged in the usual fashion: 1, Protozoa and Protozoan Infections; 2, Helminths and Helminthic Infections; and 3, Arthropods and Human Disease. Each section is prefaced by comment on the physical characters of the organisms to be discussed and their position in the animal kingdom. The style of presentation is "paragraphic," material on important parasites being arranged as follows: zoölogic name, common synonyms, history and nomenclature, geographic distribution, morphology, biology and life cycles, epidemiology, pathology and symptomatology, diagnosis, prognosis, treatment and prevention. Relatively unimportant organisms receive less extensive consideration. On the whole, the book seems to be fairly adequate; however, the section on Protozoa appears to have been prepared carelessly, repetition and poor construction being frequent. Other sections would have been benefited by more careful use of the terminology of pathology. Some of the photomicrographs are poorly prepared and selected, while the drawings and diagrams are generally excellent. Included also is a section on technical methods. Some of these are incomplete, and fixatives and stains advocated for intestinal protozoa and for tissues are not apt to meet the approval of experienced technicians. Twenty-three pages of references are listed. Authors and subjects are indexed separately. H. R.

THE HUMAN BODY. By LOGAN CLENDENING, M.D. Pp. 452; 106 illustrations by W. C. SHEPARD and DALE BERONIUS and from photographs. Third edition, corrected, enlarged and revised. New York: Alfred A. Knopf, Inc., 1937. Price, $3.75.

THIS book was written 10 years ago "in order to make intelligible some of the intricacies of the human body for the adult and otherwise sophisticated reader." The numerous changes since that time, both in medical science and in the author's opinions have led him to rewrite the present edition. His philosophy, however, and the skillfully introduced historical background remains unchanged and he has left in the jokes! The reader soon learns why it has proved useful for "collateral reading in courses in biology in young ladies' seminaries and other institutions of learning."

E. K.

NEW BOOKS.

Chemistry of the Brain. By Irvine H. Page, A.B. (Chem.), M.D., Hospital of The Rockefeller Institute for Medical Research, New York. Pp. 444. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

A Monograph on Veins. By Kenneth J. Franklin, D.M., M.R.C.P., Tutor and Lecturer in Physiology, Oriel College; University Demonstrator of Pharmacology; Assistant Director of the Nuffield Institute for Medical Research, Oxford. Pp. 410; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

Not So Long Ago. A Chronicle of Medicine and Doctors in Colonial Philadelphia. By Cecil K. Drinker, M.D., Sc.D., Professor of Physiology and Dean of the School of Public Health, Harvard University. Pp. 183; illustrated. New York: Oxford University Press, 1937. Price, $3.50.

Pediatric Urology. In Two Volumes. By Meredith F. Campbell, M.S., M.D., F.A.C.S., Professor of Urology, New York University College of Medicine, and Associate Attending Urologist, Bellevue Hospital; Consulting Urologist to the Mountainside Hospital, Montclair, N. J., Memorial Hospital, Morristown, N. J., Essex County Isolation Hospital, Belleville, N. J., and Essex County Tuberculosis Hospital, Caldwell, N. J. With a Section on Bright's Disease in Infancy and Childhood, by John D. Lyttle, A.B., M.D., Assistant Professor of Diseases of Children, College of Physicians and Surgeons, Columbia University; Assistant Visiting Physician, Babies and Willard Parker Hospitals, etc. Pp. 1116; over 1350 illustrations and 2 colored plates. New York: The Macmillan Company, 1937. Price, $15 the set.

The Endocrines in Theory and Practice. Articles Republished from the British Medical Journal. Pp. 278. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $3.50.

Vitamins and Deficiency Diseases. By Bernard L. Oser, Ph.D., Director, Food Research Laboratories, Inc., New York. (Reprint of Chapter XXXV of Hawk and Bergeim: Practical Physiological Chemistry, eleventh edition, Copyright, 1937.) Pp. 133; illustrated. Philadelphia: P. Blakiston's Son & Co., Inc., 1937.

Differentialdiagnose in der Inneren Medizin. Lieferung 3. By Prof. Dr. Med. O. Naegeli, Gew. Direktor, Der Medizinischen Universitätsklinik, Zürich. Pp. 325; 59 illustrations. Leipzig: Georg Thieme, 1937. Price, Rm. 10.80.

This third installment covers the febrile state; joint diseases; the esophagus; heart and blood-vessels; kidney and urinary tract; nervous system; and endocrine disorders. While it is obviously impossible to treat so many conditions from this point of view in the small space available, the reader will find much valuable information authoritatively stated within this short space.

International Clinics, Vol. IV. Forty-seventh Series, December, 1937. Edited by Louis Hamman, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 Collaborators. Pp. 343; illustrated, and 1 colored plate. Philadelphia: J. B. Lippincott Company, 1937.

Der Psychische Restitutionseffekt. Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion. By Dr. med. Otto Löwenstein, vorher ordentl, Professor und Direktor des Pathopsychologischen Instituts der Universität Bonn sowie leitender Arzt der Rheinischen Provinzial-Kinder-Heilanstalt für seelich Abnorme in Bonn. Nyon (Schweiz), Klinik La Métairie. Pp. 92; illustrated. Basel: Benno Schwabe & Co., 1937. Price, Francs suisses 8.00.

Die Werke des Hippokrates. Part 16. Der Samen / Das Werden des Kindes / Das Herz / Die Geistesstörung / Die Tollwut / Die Nieswurzanwendung. (On Generation; On the Nature of the Infant; On the Heart; On Mental Disturbance; On Hydrophobia; On the Administration of Hellebore.) Pp. 95. Price, Rm. 7.50. Part 17. Die Leiden / Die Krankheiten, 1. Buch. (Of Affections; Of Diseases, Book 1.) Pp. 102. Price, Rm. 8. Part 16. Uberfest von Dr. Med. Richard Kapferer, Facharzt für Phnfitalisch-diätetische Behandlung. Part 17. Herausgegeben von Dr. Med. Richard Kapferer, Bad Wörtshofen und München, unter Mitwirtung von Prof. Dr. Georg Stider, Würzburg, u. a. (To be published in 25 parts costing about Rm. 100, card binding.)

Artificial Fever. Produced by Physical Means; Its Development and Application. By Clarence A. Neymann, A.B., M.D., F.R.S.M., Associate Professor of Psychiatry, Northwestern University Medical School; Honorary Professor of Medicine, National University of Mexico, etc. Pp. 294; 68 illustrations and 21 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

The Medical Clinics of North America, Vol. 21, No. 6 (New York Number, November, 1937), Index Number. Pp. 321; illustrated. Philadelphia: W. B. Saunders Company, 1937.

This New York number is mostly devoted to a symposium on Arthritis with 26 contributions that cover an equal number of aspects of this complex subject. The opening statement of The Arthritis Problem by R. G. Snyder is appropriately the most extensive, if not the most detailed, of the lot. The remaining articles of the number are on edema in Bright's disease, diagnosis of neuroses, pre-natal care, treatment of heart disease, and epilepsy.

Der Vitaminhaushalt in der Schwangerschaft. Mit besonderer Berücksichtigung der Vitamine A und C. By Dr. Med. Gerhard Gaehtgens, Universitätsfrauenklinik zu Leipzig. (Band 24 of Medizinische Praxis.) Pp. 161; 21 illustrations. Dresden: Theodor Steinkopff, 1937. Price, Paper, Rm. 12; Bound, Rm. 13.20.

Mental Therapy. Studies in Fifty Cases, Volumes 1 and 2. By Louis S. London, M.D., Formerly Passed Assistant Surgeon (R), United States Public Health Service; Medical Officer, United States Veterans Bureau; Assistant Physician, Central Islip State Hospital, Central Islip, N. Y., and Manhattan State Hospital, Ward's Island, N. Y. Pp. 774; 22 illustrations. New York: Covici Friede, 1937. Price, $12.50 the set.

Primary Carcinoma of the Lung. By Edwin J. Simons, M.D., Member of the Staff, St. Gabriel's Hospital, Little Falls, Minn., and Lymanhurst Health Center, Minneapolis; Visiting Consultant in Medicine, Minnesota State Sanatorium, Ah-gwah-ching, Minn. Pp. 263; 30 illustrations and 1 colored plate. Chicago: The Year Book Publishers, Inc., 1937. Price, $5.00.

Genital Abnormalities, Hermaphroditism & Related Adrenal Diseases. By Hugh Hampton Young, M.A., M.D., Sc.D., F.R.C.S.I., D.S.M., Professor of Urology, The Johns Hopkins University; Visiting Urologist, Brady Urological Institute, The Johns Hopkins Hospital. Pp. 649; 379 illustrations containing 534 drawings by William P. Didusch. Baltimore: The Williams & Wilkins Company, 1937. Price, $10.00.

Lane Medical Lectures: The Mechanism of Heat Loss and Temperature Regulation. (Stanford University Publications, Medical Sciences, Vol. III, No. 4.) By Eugene F. Du Bois, Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital, New York. Pp. 95; 41 illustrations. Stanford Univ., Calif.: Stanford University Press, 1937. Price, Paper, $1.50; Cloth, $2.25.

Die Irradiation autonomer Reflexe. Untersuchungen zur Funktion des autonomen Nervensystems. By DR. ALFRED SCHWEITZER, Assistent im Department of Physiology, Middlesex Hospital Medical School, University of London. Pp. 376; 38 illustrations. Basel: Verlag von S. Karger, 1937. Price, Paper, Fr. 40; Bound, Fr. 44.

Doctors on Horseback. Pioneers of American Medicine. By JAMES THOMAS FLEXNER. Pp. 370; illustrated. New York: The Viking Press, 1937. Price, $2.75.

A Method of Anatomy. Descriptive and Deductive. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the University of Toronto. Pp. 650; 564 illustrations. Baltimore: William Wood & Co., 1937. Price, $6.00.

Therapie der Tuberkulose. Bands 1 and 2. Edited by PROF. DR. J. BERBERICH und DOZENT DR. P. SPIRO. Pp. 845; illustrated, and 1 colored plate. Leiden: A. W. Sijthoff's Uitgeversmaatschappij N. V., 1937. Price, Paper Hfl. 25.00; Bound, Hfl. 28.50.

NEW EDITIONS.

A Handbook of Accepted Remedies. Symptoms and Treatment of Poisoning. Diagnostic Procedures. Miscellaneous Information. Edited by P. J. Hanzlik, M.D., Professor of Pharmacology, Stanford University School of Medicine, San Francisco. Pp. 115. San Francisco: J. W. Stacey, Inc., 1937, for the Department of Public Health, San Francisco, J. C. Geiger, Director. Price, $1.00.

The auspices under which this booklet is published and the standing of its Editor should be sufficient guarantee of its accuracy. Many demands for the first edition have necessitated this new edition in 18 months, thus permitting the inclusion of a score or more of important new items and the omission of mercurochrome and dinitrophenol as recommended therapeutic aids.

The Surgery of the Sympathetic Nervous System. By GEORGE E. GASK, C.M.G., D.S.O., F.R.C.S. (ENG.), Emeritus Professor of Surgery, University of London; Consulting Surgeon, St. Bartholomew's Hospital, and J. PATTERSON ROSS, M.S. (LOND.), F.R.C.S. (ENG.), Professor of Surgery, University of London; Surgeon and Director of the Surgical Unit, St. Bartholomew's Hospital. Pp. 191; 49 illustrations. Second edition. Baltimore: William Wood & Co., 1937. Price, $4.50.

A Text-book of Ophthalmic Operations. By HAROLD GRIMSDALE, M.B., F.R.C.S., Consulting Ophthalmic Surgeon to St. George's Hospital; Consulting Surgeon to the Royal Westminster Ophthalmic Hospital; and ELMORE BREWERTON, F.R.C.S., Consulting Ophthalmic Surgeon to the Metropolitan Hospital; Consulting Surgeon to the Royal Westminster Ophthalmic Hospital. Pp. 322; 105 illustrations. Third edition. Baltimore: William Wood & Co., 1937. Price,. $6.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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CANCER OF THE COLON.

MALIGNANT lesions of the large bowel are now being treated surgically with such success that a review of the subject would seem timely, especially as there exists a uniformity of opinion here and abroad on the major problems in this field. Methods of surgical treatment have advanced rapidly and operative mortality has declined considerably. The numerous factors which must govern treatment vary greatly, so that the end results do not depend wholly on operative skill but also upon the extent of the disease, the general condition of the patient, and upon the percentage of patients afforded radical treatment in different clinics. Gemmill[7] has pointed out that "In this country the great mass of human ills is diagnosed and treated outside of the great medical centers, and malignancy of the colon is no exception to the rule." It was his feeling that "either due to the patient's perverseness or to the attending physician's carelessness, in not sending the patient to a hospital for diagnostic study, the patient is admitted as a last resort and often in a moribund condition."

Etiology. The observations of Junghanns[14] and Santy, Mallet-Guy and Croizat,[30] which are an extension of Lambling's conception of villous tumors, have added to our knowledge of the pathogenesis of certain of these tumors. It is generally agreed that adenomatous polyps are a frequent, if not the most common, predisposing factor in the etiology of colon cancer.

There is a familial tendency to polypósis. Rankin[26] has reported excellent examples of this familial tendency. Nystroem[23] believed that there is a hereditary tendency to polyposis in from 50 to 60%

of cases. Martin[20] believes that polyposis or adenomatosis is of serious significance. The statement of Hardy[9] that malignant changes occur in 40% of polyps substantiates Martin's feelings. The frequency with which multiple polyps are present in the bowel and the fact that intestinal polyposis is most frequently observed in the large bowel may account for the high incidence of large bowel cancer and the frequency of multiple neoplastic lesions.

Junghanns[14] found that 70% of the large bowel tumors in Schmeiden's Clinic were related to a pre-existing polyposis and Nystroem believed polyposis or adenomatosis to be associated with 63% of carcinomata of the large intestine.

Klingenstein,[15] in an interesting discussion of multiple carcinomata of the colon, stated that while not rare, the lesions were not common. Warren and Gates[35] reported 29 cases and Bargen and Rankin[2] reported 16 personal cases. It was their feeling that in each instance they were dealing with distinct, primary, malignant lesions. They state that "polyps should be considered omens of possible malignant disease of the large intestine."

Chemical and physical trauma have been considered as etiologic agents and as aggravating factors.[7] The report of Reed and Anderson[28] on the relationship of amebiasis and cancer of the colon is worthy of note. They call attention to the fact that amebic lesions of the colon have been mistaken for carcinoma and that cancer has been mentioned by various writers as a possible sequel of amebic dysentery. These authors report 4 cases of amebiasis in which carcinoma of the colon followed and accompanied the amebic infection. The coincident sites for election and the similarity of symptoms make the differential diagnosis difficult.

We have recently observed a patient with extensive ulcerative colitis and carcinoma of the hepatic flexure. The malignant lesion had gone undiagnosed for some time because it was believed that the patient's symptoms were due to the ulcerative colitis. Yeomans[37] has called attention to the occurrence of amebic granuloma as one of the protein manifestations of amebiasis. These lesions may be acute or chronic and may closely simulate carcinoma of the colon and rectum. The differential diagnosis without biopsy may be exceedingly difficult. Reed and Anderson state that perhaps "the amebic lesions, in the presence of poorly understood predispositions, increase the facility of cancerous transition." They raise the question of whether vitamin G and the intrinsic gastric hormone play a part in this predisposition and whether deficiencies of vitamins G and B effect the course of the ulceration and the eventual occurrence of malignancy. The frequency with which polypoid and adenomatous growths follow amebic lesions in the colon and rectum is of more than casual significance.

Incidence. There is little difference of opinion in regard to the incidence of the disease in various portions of the large bowel. In Judd's[13] series 26% of the tumors were in the ascending colon and cecum, 20% in the transverse colon and flexures and 54% in the descending colon and sigmoid. Lahey's figures[17] were identical, while Rosser's[29] percentages were 32, 19 and 49 respectively. Rosser collected data on 1564 colon cancers reported by 6 authors and found the incidence in the location of the lesions similar to those already given. The 6 authors included rectosigmoid tumors, in fact tumors in this location were more frequent than at any other site.

Symptoms and Signs. The symptoms and signs of large bowel malignancy, especially in the early stages, are often so indefinite that as David[5] has said, they may be completely overlooked. Even the most intelligent patient may not realize that anything is wrong until the lesion has grown to considerable size. From the beginning of the disease to the first symptoms may represent, as a rule, many months.

In more than two-thirds of the cases studied by Rosser, cancer of the cecum and ascending colon simulated chronic appendicitis. The main differential diagnostic feature was a moderate or severe anemia in 65% of his cases. Fifteen per cent of the cases reported by Priestley and Bargen[24] and 18% of Brindley's[3] series had been subjected to appendectomy.

A tumor mass in the right lower quadrant is not absolutely indicative of a malignant lesion. Benign tumors such as the argentaffine tumor reported by Lee and Taylor[18] may be found in this region. An old appendiceal abscess may simulate cancer. Barium enema may, or may not, give definite evidence of a cecal defect early in the disease.

There is little tendency for these right-sided colon tumors to cause intestinal obstruction. The lesions are usually not encircling, and the fecal stream is still liquid in this portion of the bowel. Rankin[26] has called attention to the infrequency of obstruction in these tumors and Rosser[29] has not encountered a single instance of obstruction or even constipation in his series. In contradistinction to this 6% of his patients with right-sided tumors had diarrhea and 78% had localized pain and indigestion. Blood was observed in the feces by the patient in 14% of the cases.

It may well be restated that in any patient past 30 years the occurrence of a persistent, unexplained anemia with or without a right lower quadrant mass should be studied for a cecal or ascending colon lesion. This is true whether the symptoms suggest chronic appendicitis, peptic ulcer, or cholecystitis.

In the transverse colon constipation is probably the outstanding symptom and the tendency to constipation increases as the location of the tumor approaches the rectosigmoid junction. This is due to the fact that the tumors of the mid-colon and descending and sigmoid colon are, as a rule, encircling lesions which tend to constrict the lumen. A change in the bowel habits may be the first, and often the only, sign of malignant disease until acute obstruction is precipitated.

The constipation may be terminated by periods of diarrhea to be followed again by constipation. The periods of diarrhea too frequently have led to the diagnosis of colitis. This is especially true when the carcinoma is associated with a polypoid lesion as Nystroem[23] has pointed out. Manson-Bahr[19] called attention to the fact that diarrhea may be an expression not only of malignant disease and colitis, but also of intussusception, polyposis, and diverticulitis. Non-malignant lesions causing intussusception are more frequently encountered in young people, but as Reed and Anderson[28] point out, intussusception may occur following dilatation and hypertrophy of the bowel above the lesion.

Rosser[29] found that patients with tumors of the mid-colon frequently had a severe anemia and in this way were similar to tumors of the right colon. Blood in the stools was observed in 19% of the patients he studied with mid-colon malignancies. In the rectal malignancies, Rankin[26] found that 85% of the patients had bleeding at one time in the disease, a finding which is substantiated by the findings of Ramirez-Calderón.[25]

Colic is an outstanding symptom in left-sided malignancy. The initial pain may occur on the right side due to distention of the right colon. Associated with the colic is a varying degree of flatulence. The lower the tumor in the left side the more mild and the later is the appearance of colic.

Constipation, continuous or intermittent; afebrile, intermittent or continuous diarrhea; colic and the presence of blood in the stools are so suggestive of left colon cancer that every patient with all or part of these symptoms should be subjected to the closest scrutiny. The appearance of hemorrhoids in an individual past middle-age also calls for a careful digital and proctoscopic examination.

Special Examination. In any individual, regardless of age or sex, presenting the aforementioned symptoms, in part or in whole, certain special studies are mandatory. The examination of the feces for blood and ameba, and a careful hematologic examination should, of course, be routine. The roentgenologic exploration of the colon by the barium meal, together with contrast studies, are of the greatest importance. As Dixon[6] has said, these studies are responsible "for the greatest recent advancement in the control of carcinoma as they have made possible the detection of an increasing number of early lesions." It is of the greatest importance that the study be made by a competent roentgenologist, and that the fluoroscopic study be made under the most favorable circumstances.

For the low sigmoid and rectal tumors direct observation is the easiest method of diagnosis. No study of the colon is complete without a proctoscopic and sigmoidoscopic examination. A biopsy can often be obtained for histologic study. The more frequent use of digital examination as a part of a complete physical examination would lead to earlier diagnosis in many instances.

Even though the surgical literature on the subject has been voluminous, the number of late cases observed in the surgical clinic demonstrates that physicians, in general, still frequently fall short in their responsibilities to these patients.

Preliminary Treatment. Many of the patients when first seen are suffering from varying degrees of intestinal obstruction. The small bowel may or may not be distended. Vomiting may or may not have occurred. Wangensteen[33] believes that vomiting is not uncommon in complete obstruction from cancer of the colon, while David[5] believes that it rarely if ever occurs. Our own experience coincides with that of Wangensteen. Dehydration and a disturbance in the electrolyte balance may be due to vomiting, to the fluid contained in the dilated bowel, and to a restriction of fluid intake even though the obstruction is incomplete.

Where marked distention is present the decision must be made between a temporary colostomy, or enterostomy, or decompression by suction drainage. While the method of Wangensteen and Paine[34] is without doubt of real value, internal drainage by the method to be reported by Abbott and Johnston[1] provides for complete bowel evacuation above the point of obstruction. It is, we believe, a great advance in the preparation of obstructed patients for operation.

The pre-operative use of blood transfusions in all patients suffering from anemia is well recognized but their use in many of the patients with left-sided tumors who are not very anemic is equally important. Miles[21] and others have for some years emphasized the beneficial effect of pre-operative and postoperative blood transfusions to patients with rectosigmoidal and rectal cancer.

Pre-operative vaccination of the peritoneum in patients without acute obstruction is becoming a more accepted procedure. The excellent work of Steinberg,[31] Herrmann,[10] Weinstein,[36] and of Milone[22] has shown that the incidence and extent of the peritonitis which may occur following radical removal of the tumor can be in part controlled by pre-operative peritoneal vaccination.

The radical removal of the tumor is never an emergency procedure so that following internal or external decompression the surgeon has sufficient time properly to prepare the patient. The late Dan Jones[11] very wisely stressed the fact that an empty bowel, which had been thoroughly cleansed, was one of the best safeguards against postoperative peritoneal infection.

Where preliminary external colostomy becomes necessary there is as yet no unanimity of opinion as to the location of the temporary anus. Rayner[27] believes that while cecostomy is not the ideal operation when the cancer is in the distal colon, it works sufficiently well and can be depended on to save the patient's life in the emergency. It is nearly always easy to perform, "it leaves the field for the later operation of resection undisturbed and the surgeon unhampered." The performance of the colostomy close to the obstructing lesion may be regretted at the secondary, or major operation.

On the other hand, Rankin[26] believes that in the left-sided tumors a transverse colostomy is often the procedure of choice. The difference of opinion is the result of the fact that very often a cecostomy fails completely to empty the bowel and although it may be lifesaving in the emergency it fails to permit of an empty clean bowel between the drainage point and the obstruction.

There still is considerable difference of opinion as to whether an exploratory laparotomy should be done at the time of the initial colostomy. Rayner[27] favors exploration unless the condition of the patient is desperate at the time of the cecostomy. It is our impression that careful abdominal exploration at the time of the initial colostomy has frequently proved too much for the patient. This is especially true when distention is excessive. With the use of suction drainage, especially by the method of Abbott and Johnston,[1] sufficient decompression may be obtained and the general state of the patient so improved as to make colostomy and exploration possible at the same time with complete safety to the patient.

Rayner[27] gives 3 advantages of exploration: 1, The diagnosis of colonic obstruction can be verified and secondary obstructions will not be overlooked; 2, the information gained at exploration permits one to better plan the more radical operation if this can be done; 3, exploration permits better exposure of the cecum so that "blind cecostomy is not necessary." Gemmill,[7] however, does only the cecostomy at the first stage and delays exploration until the patient is in good condition. There is sufficient reason for a difference of opinion and the most experienced surgeons rarely follow a single technique.

The choice of the anesthetic for the initial operation must be left to the surgeon. We prefer spinal or local anesthesia. Rayner[27] prefers spinal anesthesia as does Jones,[12] "because it provides excellent relaxation and a quiet abdomen."

When the condition of the patient following colostomy has improved and the bowel is thoroughly cleansed the radical procedure should be considered. The viewpoint of Miles,[21] that the most radical operation is the operation of choice, is gradually becoming accepted. There are those who believe that the limited operations, with their lower operative mortality, are to be preferred, but we agree with Jones[12] when he states that, "too much attention has been paid to operative mortality when a decision is made regarding which type of operation is to be used." Furthermore, differences in mortality depend not only on the type of operation but on the condition of the patient, the extent of the disease and upon the skill of the surgeon. In addition to these factors, one must consider what a surgeon considers an operable lesion to be. This frequently varies with experience. If too much stress is placed on operative mortality, the per cent of operability will decline and thus many patients will be denied an opportunity for cure.

There are many surgeons who believe radical colon surgery contraindicated in the presence of metastasis, especially to the liver. Koch,[16] Gordon-Watson,[8] Jones[12] and others are not in agreement with this conception, for it is well known that radical resection will often permit an "endurable existence for four or five years." Every liver nodule is not necessarily a malignant metastatic deposit, angiomata and fibromata are also found in the liver as Gordon-Watson has indicated. Jones[12] has aptly said that "It is an error to perform small operations for small cancers and big operations for big cancers; perhaps the results would be better if the plan were reversed."

We shall not attempt to review the many operative procedures now used for malignant lesions of the colon. So many modifications of even the standard operations now exist that such a review would be useless. There are, however, certain generalizations in regard to operation which we believe to be valuable.

Local resection and anastomosis of right-sided lesions is to be condemned. For tumors of the cecum, ascending colon and hepatic flexure we believe that a right colectomy, and anastomosis of terminal ileum to transverse colon to be the operation of choice. Rankin[26] believes that ileocolostomy should be done at the first stage and resection at a second operation 2 weeks later. Wakeley and Rutherford[32] have reported 14 such operations without a death. Rayner[27] favors the operation as a one-stage procedure.

In lesions of the transverse colon and splenic flexure resection and anastomosis following a preliminary colostomy seems to be the operation of choice.

In the sigmoid there is some variation of opinion. The Mikulicz operation still has many advocates. The Rankin obstruction resection, which is in reality a refinement of the Mikulicz operation, is a very useful procedure. It permits of wide excision of the growth and mesentery at the major operation and thus overcomes what we believe to be the major disadvantages of the original operation. This is in accord with the observations of Burt.[4]

Many surgeons still prefer resection and end-to-end anastomosis for lesions of the mobile sigmoid. This procedure should not be done without a preliminary colostomy and thorough cleansing of the bowel.

In the lesions of the pelvic colon and rectosigmoid junction the abdominoperineal resection in one or two stages is without a doubt the operation of choice. Jones[12] favors the one-stage operation because: 1, The patient is subjected to only one operation; 2, the operation is more easily performed without the presence of adhesions from the previous operation and it can be performed more expeditiously and with less shock; 3, if a growth is inoperable at the first operation it is generally inoperable at the second operation.

Nevertheless, many surgeons prefer the two-stage operation because they feel it permits of rehabilitation and is thus safer. It is the procedure of choice for most surgeons doing abdominoperineal resections.

No attempt has been made to cover the literature on anorectal carcinoma, or the literature on irradiation for malignancy of the colon. The lesions of the colon metastasize slowly and are, therefore, usually amenable to surgical therapy. The end-results of surgical treatment will depend upon the time at which operation is undertaken, the extent of the disease, and the thoroughness of the surgical procedure.

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OPHTHALMOLOGY.

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TREATMENT OF TOBACCO—ALCOHOL AMBLYOPIA.

During the past several years progress has been made in the treatment of tobacco and alcohol amblyopia. Accurate diagnosis is imperative, for a patient complaining of slowly failing vision and giving a history of the use of moderate or excessive amounts of tobacco and alcohol may have a brain tumor, meningo-encephalitis, poisoning by one of the heavy metals or a metabolic disease such as diabetes or leukemia. Campbell[1] has outlined a proper course of investigation: careful and detailed history, neurologic examination, spinal puncture, otolaryngologic examination, roentgenograms of the optic foramina and teeth, search for foci of infection, diseases of the blood, syphilis, and tuberculosis. One might add analysis of the urine for lead and arsenic, and examination of the perimetric fields. Carroll[2a] has pointed out the necessity of differentiating the disease from senile macular degeneration.

In this country there seems to be a definite clinical entity of tobacco-alcohol amblyopia, at least most of the persons affected are both moderately heavy smokers and drinkers. However, Carroll and Franklin[3] have reported an uncomplicated case of tobacco amblyopia and an uncomplicated case of alcohol amblyopia, in both of which there were centrocecal scotomas. They noted that in Great Britain tobacco is considered the offending toxin and in France alcohol. At a special meeting of the Ophthalmological Society of the United Kingdom held in 1887, to discuss the matter, it was concluded that the amblyopia was due to the tobacco, that alcohol was not the direct causal agent, and that depression of health was an accessory influence. Fifty years later these "accessory influences" are just beginning to be understood. Usher,[15] quoted by Riddell,[12] found that subjects of tobacco amblyopia did not consume more tobacco or alcohol than many other smokers or drinkers of the same age who did not have any amblyopia.

The clinical picture is that of a man 50 to 60 years old who states that his vision seems misty and that he cannot recognize the faces of his friends. The diminution of his visual acuity has been insidious, and there may be slight pallor of his optic disks. The disease is not rare. It comprises, for example, 1% of the cases seen at the out-patient department of the Edinburgh infirmary,[14] and 0.3 to 0.5% of the patients newly admitted to the eye clinic of the Massachusetts Eye and Ear Infirmary.[2a]

Traquair[14] has described for tobacco amblyopia a centrocecal scotoma with 1 or 2 dense nuclei within it, lying between the point of fixation and the blind spot, and demonstrable with small test objects at 1 meter. This same refined technique applied to a group of cases of uncomplicated alcohol amblyopia might yield characteristics helpful in differentiation of the tobacco from the alcohol groups, although Lillie[9] has stated that in his experience the size and shape of the different scotomatous defects depend on the stage the condition has reached, and none is pathognomonic of any specific etiologic factor.

A rational therapy based on a clear understanding of the disease is not possible at present. Some writers[14] state that tobacco exerts a direct toxic action on the ganglion cells of the retina, and that optic atrophy is secondary to atrophy of these cells. Friedenwald[6] has been unable to confirm this. Others[5b,11] hold that tobacco causes amblyopia by constricting the vessels supplying the papillomacular bundle. The form of therapy will vary according to whether one accepts the first or second of these concepts.

Traquair,[14] favoring the first of these, has his patients stop the use of tobacco and restores them to as healthy a condition as possible. He recommends that they drink large quantities of water and that they use some laxative medicine. In his opinion "There is no specific treatment which can be directed toward the affected nerve elements. The use of vasodilators such as sodium nitrite has been advocated upon the hypothesis that the affection is due to vascular constriction. No evidence has as yet been brought forward to show that this hypothesis is correct or that the treatment is efficacious."

Duggan[5a] believes that tobacco causes amblyopia by constricting the vessels supplying the papillomacular bundle. In support of his contention he refers to the experimental work of Wright and Moffat,[18] who demonstrated that smoking cigarettes caused a drop in temperature at the finger tips and a slowing of the blood flow in the capillaries of the nail folds, and to the concept of Sulzburger,[13] who suggested the possibility that the vascular system of man may become sensitized to allergens derived from tobacco. Duggan recommends the use of vasodilators and prefers the intravenous injection of 100 mg. of sodium nitrite as nitroscleran for 6 to 10 days. Under this treatment, 88% of his patients attained 20/30 vision in one or both eyes in about 18 days. He favors abstinence, for those of his patients who smoked during treatment recovered more slowly than those who did not. In a series of 8 cases Cordes and Harrington[4] duplicated his results, finding improvement in all, and more rapid improvement than could have been expected from abstinence alone.

Carroll's[2a] treatment consists in abstinence, though a few of his patients improved without giving up their tobacco and alcohol, and a few failed to improve in spite of abstaining. He gave several patients inhalations of amyl nitrite and 4 a single intravenous injection of a solution containing sodium nitrite. One of the latter seemed to have a slight temporary improvement in vision, but no change occurred in the others. It should be noted that Duggan recommended not 1 but 6 to 10 such injections.

In Carroll's opinion, chronic retrobulbar neuritis may be caused by either tobacco or alcohol separately or by the two together. In this country, usually the patient is found to be using generous amounts of both and there may be difficulty in deciding which is the more important factor. He[25] has recently reported 10 cases of the clinical syndrome of tobacco-alcohol amblyopia occurring in patients with alcoholic type of pellagra or polyneuritis. These patients smoked in moderation but were heavy drinkers, imbibing 1 to 3 quarts of alcoholic liquor a day, and in every case diet had been inadequate. Treatment consisted in lowering the intake of alcohol and maintaining a diet high in vitamin B complex. While he did not describe a definite regimen, he mentions in his case histories intramuscular injection of liver extract and of vitamin B_1 concentrate, and addition to the diet of brewer's yeast, wheat germ (Embo), and Vegex.

At present a number of investigators[7,8,17] offer evidence that ethyl alcohol has no direct action on the optic nerves. Optic and retrobulbar neuritis occur when the excessive and prolonged use of alcoholic liquor has created a nutritional disturbance and beriberi or pellagra-like syndromes. These are regarded as due to lack of vitamin B_1 and B_2, respectively.

Moore[10] reports that in Nigeria he has seen thousands of cases in various stages of the clinical picture of misty vision, sore tongue, dry, itchy scrotum. After 2 months there is optic atrophy and there may be great loss of vision. The disease is the result of deficiency in the diet. In a school of 80 children living on a low-protein diet where every girl had the disease and not one boy, the boys were supplementing their diet with land crabs which were plentiful and which they caught and roasted, while the girls were kept in seclusion and could not have them. Moore believes the proteins afforded the missing link in the natives' diet and that the specific factor was vitamin B. The disease was dramatically amenable to marmite and to yeast, which are rich in vitamin B complex. Vitamins A, C and D added to the diet possessed no curative properties.

Wagener,[16] in a review of literature on the rôle of vitamin B in nutritional diseases of the eye, concluded that, "while clinical reports of ocular lesions dependent on or associated with deficiencies of vitamin B_1 and B_2 are rather scattered as yet, in this country at least, it would seem that enough clinical and experimental data are accumulating to indicate that deficiencies of these vitamins may play a more important rôle than is generally appreciated in the causation of acute and chronic affections of the optic nerves."

For a patient presenting the clinical syndrome of tobacco-alcohol amblyopia, current opinion favors the following therapeutic measures:

1. *Abstinence From the Drugs.* This is necessary in regard to tobacco, but not imperative for alcohol if adequate diet is supplied and it is used in moderation.

2. *Eliminative Measures.* Those commonly recommended are increased fluid intake, laxative medicines and pilocarpine sweats. One might question the value of these time-honored remedies, for there is no evidence that they eliminate the poisons of tobacco or hasten the excretion or oxidation of alcohol. The pilocarpine sweats may serve a useful purpose in their vasodilating effect.

3. *Vasodilators.* Those having a transient effect are amyl nitrite inhalations and acetylcholine in intramuscular injections of 0.1 gm. A more prolonged effect is obtained by intravenous injections of sodium

nitrite in 0.1 gm. doses, and it is recommended that this be given daily for about a week.

4. *Nourishing Diet.* Because idiosyncrasy and lowered nutritional state are factors predisposing to poisoning by tobacco, a nourishing diet should aid in recovery. Alcohol, while not acting as a direct poison on the optic nerves, interferes with nutrition to the extent that it leads to inadequate diet and deficiency of the vitamin B complex. The diet, besides having a sufficient calorie content, should contain large amounts of yeast, wheat germ, green vegetables and vitamin B_1 concentrate. This can be supplemented with intramuscular injections of liver extract.

The treatment of tobacco-alcohol amblyopia in the near future may be placed on a basis less empiric and somewhat more scientific. It will require that the chief offender be determined, whether it be the tobacco or alcohol. For the tobacco cases, the use of vasodilators holds promise if the early favorable reports of its originators can be confirmed by others. For the alcohol cases the problem of nutrition becomes foremost, with the vitamin B complex as the specific element most needed to be restored to the diet.

C. W. Rucker, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 20, 1937

Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes. F. C. Dohan and F. D. W. Lukens (Cox Institute, University of Pennsylvania). Experiments were reported which showed that adrenal cortical extract was capable of restoring to a considerable extent the diabetes of adrenalectomized-depancreatized animals. The factors suggested as favoring this response (species, salt intake, estrus, adrenal remnants, etc.) are noted. An increase in the urinary excretion of glucose and nitrogen after cortical extract was also observed in two hypophysectomized-depancreatized cats.

Tumors of Peripheral Nerves in Fish. Balduin Lucké (Laboratory of Pathology, University of Pennsylvania). While a considerable variety of tumors have been observed in many different species of marine fish, hitherto no kind of tumor has been found with sufficient frequency to make it readily available for study. The abundance of fish in the waters about the Tortugas and the exceptionally favorable collecting facilities of the Laboratory afforded the opportunity for discovering that certain kinds of tumor commonly occur in several species of snappers (*Lutianidæ*). These tumors arise in the corium or subcutaneous tissue, whence they project outward as flattened oval masses, stretching the covering epiderm to a delicate membrane devoid of scales. They vary in size from small nodules to conspicuous masses over 4 cm. in diameter. The tumors are distributed along the course of the peripheral nerves. Usually but one growth is present, though two, three or even four tumors may occur. They are firm and resilient in consistency, and have a white, usually moist cut surface, which is nearly homogeneous in some, striated or whorled in others. At their base some are sharply delimited, others infiltrate the subjacent tissue. However, despite the rather uniform naked-eye appearance of the tumors, there is considerable variation in their structure. They are composed of cells resembling fibroblasts, of fibrillar tissue and homogeneous intercellular substance, the proportion of these components varying greatly. Some are richly cellular, others are fibrous or even partly hyaline; whether cellular or fibrillar they usually have a distinctly fasciculated makeup, the cells being arranged in interlacing bands and whorls. In many tumors their oval nuclei are grouped in a peculiar manner, forming more or less parallel rows or palisades, between which lie dense masses of fibrils or nearly homogeneous tissue. In places there are structures resembling nerve fibers. Areas of degeneration, hyaline or mucinoid, are common in the larger growths. The more cellular tumors somewhat infiltrate the adjacent tissue; the more fibrillary growths are sharply circumscribed though usually not encapsulated. No metastasis has been observed.

Neoplasms of this kind were found in 39 fish belonging to three species of snappers, the gray snapper (*Lutianus griseus*), dog snapper (*Lutianus jocu*) and schoolmaster (*Lutianus apodus*). All the specimens were mature and of average or large size. Though many fish of other families were examined, no tumors of this kind were observed. Transmission experiments were not successful, the inoculated fish dying within a few days, whether from operative procedures or from other causes is not certain. It is possible that a different technique may give better results.

The tumors here reported closely resemble the complex group of human neoplasms arising from the sheaths of nerves. Like them they show the palisade arrangement of nuclei characteristic of this group. An additional point of resemblance to neurogenic tumors is the occurrence of structures resembling nerve fibers.

The relative ease with which these tumors may be secured in the Tortugas (and possibly elsewhere in tropical waters) renders them very favorable material for the study of an important group of neoplasms.

The Origin of the "Off" Response in the Optic Pathway. H. K. Hartline (Johnson Foundation, University of Pennsylvania). Different optic nerve fibers of the vertebrate eye respond differently to illumination of the retina. Some (about one-quarter) respond only to cessation of illumination; they discharge no impulses at all during illumination. Reillumination abruptly stops whatever discharge may be present. The more primitive eye of the scallop, Pecten irradians, might also be expected to give "off" responses, for the animal exhibits a vigorous "shadow reaction." The Pecten eye is unique in structure, possessing a double layer of sense cells, each with its separate optic nerve branch. Axones of the proximal sense cells discharge impulses only during illumination of the eye. Axones of the distal cells (which have been described as primary sense cells) discharge impulses only in response to cessation of illumination. These "off" responses are indistinguishable in character from those in the vertebrate optic nerve. If these distal cells are truly primary sense cells, the possibility is raised that certain of the rods or cones (or both) in the vertebrate retina respond only to cessation of light. However, in the vertebrate retina an "off" response elicited by turning off one patch of light is abruptly stopped by turning on an adjacent patch. This strongly suggests that the "off" response originates at the point of convergence of the adjacent pathways (presumably the ganglion cell) rather than in the sensory layer. It is possible that "off" responses must be considered a property of certain nerve cells in general (either sensory cells or ganglion cells), which discharge impulses in response to a shift in their equilibrium in a direction opposite to that which usually causes activity.

Observations on the Motor Activity of the Obstructed Small Intestine Made During the Course of Treatment by Intubation. W. Osler Abbott, Louis Zetzel and Paul M. Glenn (Gastro-Intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania). The method of intubating the small intestine by the use of a double-lumened tube bearing at its tip a distensible balloon has been modified by Abbott and Johnston for use in the treatment of acute intestinal obstruction. In the employment of the technique we have made certain observations concerning the motor activity of the partially and completely obstructed human jejunum and ileum. These consist, 1, of balloon tracings on a kymograph indicating the degree of intestinal activity and response to internal pressure; 2, of fluoroscopic observations on the rate and character of the tube's passage; and 3, occasionally of fluoroscopic observation of the behavior of small amounts of barium sulphate suspension injected through the tube into the gut lumen proximal to the lesion.

These studies may be summarized by the statements, 1, that in every case (save one of uremia), in which peristalsis was absent or markedly diminished, whether from mechanical or paralytic causes, activity increased with decompression of the distended intestine; 2, that although reverse peristalsis occurs commonly in the duodenum we have never seen it from the ligament of Treitz to the ileocecal valve; 3, that proximal to an obstruction a fairly regular series of changes in the motor phenomena takes place consisting of transient hypertonicity of the gut, followed later by distention which involves an area that extends progressively orad as time passes; 4, that as effective peristalsis requires initial relaxation, the amplitude of peristalsis is greatest in a zone that likewise moves progressively orad being located in that area of the intestine in which the muscle fibers are beginning to be stretched by the advancing distention; and 5, that in view of the amplitude and direction of peristalsis the orad flow of intestinal contents is probably governed by the gradient of internal pressure.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
MARCH, 1938.

ORIGINAL ARTICLES.

THE INFLUENCE OF MUCIN UPON THE ABSORPTION OF IRON IN HYPOCHROMIC ANEMIA.

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Mucus has a number of obvious qualities which can act to protect surface membranes of the body: mucus binds acids, holds foreign bodies (bacteria), can absorb an enormous amount of water, and holds enzymes of the stomach and intestine (Boldyreff[1]). Boldyreff believed that if present in large quantities mucus can seriously hinder digestion, weakening the action of digestive ferments and slowing down absorption of digested food. Davies,[2] among others, has called attention to the increase of mucus in the gastric contents of patients with chronic hypochromic anemia and achlorhydria. It has often been assumed for various reasons that the absorption of iron from the intestine of these patients is defective. Although the presence of mucus has not been considered a factor in the malabsorption of iron, the possibility is apparent. The following observations were made to ascertain whether or not iron fed to patients with hypochromic anemia in the presence of a large amount of mucin would be utilized to a less extent than iron given alone.

Method. Ten cases of hypochromic anemia, or iron deficiency, were studied (see Table 1). Although blood loss was probably the principle cause of iron deficiency in all patients, blood loss had ceased before the periods of observation began. The patients were given a basal diet which was rather low in iron. A summary of the hemoglobin and reticulocyte percentages and the amount of iron and mucin administered is recorded in Table 2. Reticulocytes were counted daily upon smears of capillary blood stained supravitally with brilliant cresyl blue and counterstained with Wright's stain. Venous blood was obtained every other day, and prevented from clotting by oxalate. Upon this blood the red blood cell count, hemoglobin percentage, hematocrit (cell volume), mean corpuscular volume and mean corpuscular hemoglobin concentration were determined, according to the method of Wintrobe. The hemoglobin percentage was determined with the Sahli apparatus calibrated so that 100% hemoglobin was equivalent to 15.6 gm. per 100 cc. or 20.9 volumes % oxygen capacity (Van Slyke).

"Gastric Mucin"* was prepared in suspension of 9 to 15%. The ferrous sulphate was given in 5% glucose solution, excepting when over 0.1 gm. three times daily was given, when it was administered in tablet form.

Results. In all cases in which mucin and iron were administered together (Cases 1, 2, 3, 4, 5), there was evidence that the mucin inhibited the utilization of iron. The criteria on which this conclusion is based are as follows: when a given amount of iron was mixed with mucin and administered daily for about 10 days and when the same amount of iron without mucin was then given daily during

TABLE 1.—SUMMARY OF CASES.

Case No.	Age.	Sex.	Diagnosis and etiologic factors.
1	68	M	Hypochromic anemia of blood loss from duodenal ulcer. Normal gastric acidity.
2	14	F	Hypochromic anemia of blood loss from gastric ulcer. "Chlorosis." Normal gastric acidity.
3	37	F	Hypochromic anemia of blood loss from duodenal ulcer.
4	51	F	Hypochromic anemia of blood loss from duodenal ulcer. Asymptomatic tertiary syphilis. Uterine fibroid (bleeding). Normal gastric acidity.
5	45	F	Hypochromic anemia of blood loss from duodenal ulcer.
6	67	F	"Idiopathic" hypochromic anemia. No history of blood loss. Poor diet. Arteriosclerotic heart disease. Gastric anacidity after the injection of histamine.
7	52	F	"Idiopathic" hypochromic anemia. Menorrhagia. Dysphagia. Gastric anacidity after the injection of histamine.
8	22	M	Hypochromic anemia of blood loss from gastric ulcer. Normal gastric acidity.
9	64	F	"Idiopathic" hypochromic anemia. No history of blood loss. Bronchopneumonia, healing. Gastric anacidity after the injection of histamine.
10	57	M	Hypochromic anemia of blood loss from hemorrhoids. Gastric anacidity after the injection of histamine.

(NOTE: Bleeding ceased in all cases before the periods of observation began.)

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* Obtained from Frederick Stearns & Co., Detroit.

TABLE 2.—DATA OF CASES OF LYMPHATIC LEUKEMIA WITH PULMONARY INVOLVEMENT.

Case No.	Initials. Sex. Age (yrs.).	From onset of disease to appearance of pulmonary symptoms (mos.).	Duration of life after pulmonary involvement (mos.).	Roentgen findings.	Roentgen therapy.	Biopsy, autopsy or other result.	Comments on pathologic findings.
1	M. J. W. M 26	Primary pulmonary onset	2	Fluid left chest	None	No biopsy. Blood studies indicated lymph. leuk.; also autopsy	Tumor masses reaching thymus and involv. hilar nodes, both lungs, and upper lobe left lung.
2	E. H. M 19	18	1	Bilateral pleural effusion	None	Sternal bone marrow. Differential blood counts. Autopsy revealed aleuk. and lymph. leuk.	Bilateral pleural effusion. Interstitial pulmonary infiltration with lymphoblasts and lymphocytes
3	W. M. M 63	9	7	Dense hilar shadows. Prominent beaded pulmonary markings	Deep	No biopsy. WBC 163,000; 8% lymphocytes. No autopsy	Miliary disseminations through both lungs
4	E. R. M 56	2½	3½	No record	None	No biopsy. WBC 488,000; 97% lymphocytes. Lymph. leuk., generalized lymph. hyperplasia	Chylous hydrothorax on left
5	F. C. F. M 79	12	1	Pleural effusion on left	None	WBC 295,000; 50% lymphocytes; 45% lymphoblasts. Autopsy: lymph. leuk., leuk. infiltr. of lungs	Lungs show perivascular leukemic infiltration, also chr. fibrous tb.
6	W. C. M 69	36	1	Pleural effusion on left	None	None. WBC 840,000; 98% lymphocytes. Pleural effusion on left; enlarged hilar lymph nodes	Small amount fluid on right. Histologic picture—diffuse cellular pulm. infiltration
7	T. H. M 53	11	20	Hilar lymph node enlargement and tumor masses in mediastinum	Deep over chest and superficial nodes; good results	Cervical node Jan., 1931. Axillary node, April, 1931. Died of lobar pneu. elsewhere. Partial autopsy	Autopsy findings not conclusive. Clin. and lab. findings favor diagnosis aleuk. lymph. leuk.
8	J. C. M 70	24	24	Jan., 1933: chest neg. Aug., 1934: Bronch infiltration, right, middle of lower lobe, also nodular areas	Deep to abdomen and chest	Cervical node, 5-18-34. Diag. lymph. leuk. WBC 40,000 to 102,500 majority of cells lymphocytes. Bronchial nodes, enlarged right lower, show extensive involvement. Bilat. pleural effusion	Extensive involvement parenchyma right lung and pleura
9	H. G. M 64	132	4	Hilar lymph node involvement	Several courses of deep	Sternal biopsy. WBC 20,000 to 283,000, greater portion are lymphocytes. Involv. hilar nodes with infiltration of peribronchial tissue	Long duration of disease with pulm. involv. late in course of disease. Diffuse pulm. infiltration microscopically
10	G. H. M 53	36	1	Large mass in anterior portion of right hilus compressing superior vena cava	Chest and nodes. WBC fell from 900,000 to 300,000	Axillary lymph node showed lymph. leuk. Blood films indicated lymph. leuk. No autopsy. Sternal marrow biopsy: 90% large and small lymphocytes	Marked venous engorgement, vessels of neck, upper chest, both anterior shoulder regions. Dyspnea marked
11	W. R. M 23	Primary	2½	Widened mediastinal shadow, right pleural effusion	Three courses to chest	Biopsy of imbedded pleural fluid sediment diagnosed lymphoblastoma	Probable prim. pleu. involvement with sec. involv. of mediastinal nodes. Nodes soft, almost caseous, first thought to be tb.

TABLE 3.—DATA OF CASES OF LYMPHOSARCOMA WITH PULMONARY INVOLVEMENT.

Case No.	Initials. Sex. Age (yrs.).	From onset of disease to appearance of pulmonary symptoms (mos.).	Duration of life after pulmonary involvement (mos.).	Roentgen findings.	Roentgen therapy.	Biopsy, autopsy or other result.	Comments on pathologic findings.
12	M. J. F 16	Primary pulmonary onset	4	Pleural effusion on left	Not well tolerated	Cervical lymph node: lymphosarcoma. At autopsy left pleura greatly thickened and infiltr. with tumor cells	Diffuse tumor infilt. left lung. Diaphragm adherent to left lung. No mediastinal lymph node involv.
13	M. S. F 42	36	3	Pleural effusion on right	Courses from Aug., 1922, to May, 1923	Biopsy from tissue removed at abdominal operation: lymphosarcoma	Microscopic study: diffuse infilt. into lung tissue of small, discrete, nodular type
14	M. E. F 56	4	1	"Chronic fibrous tb., right lung"	Radium and Roent. used	Skin-biopsy: diag. mycosis fungoides. Autopsy: localized nodules both lungs. Tumor mass, apex left lung	Microscopic examination: localized areas of infiltration replacing normal lung structure
15	J. T. M 53	5	Terminal	Chest film pronounced negative Nov. 16, 1931	17 treatments. Response poor	Cervical lymph node diagnosis: reticulum cell sarcoma. Autopsy: coëxisting healed pulmonary tb. Serosanguinous fluid both pleural sacs.	Microscopic findings: circumscribed collections of tumor cells scattered through lower lobes, both lungs. Mediastinal nodes involved
16	J. J. M 39	13	3	Sept. 9, 1933: diffuse mottling through both lungs suggesting tb.	Irrad. over 2 mos. period, 1933. Again few treatments in hosp. before he became too ill	Cervical node: lymphosarcoma. At autopsy: bilat. pleu. effusion. Both lungs diffuse infiltration	Microscopic findings: peribronchial and perivascular infiltration in lungs. Pleura thickened and studded with small tumor nodules
17	G. H.* M 45	24	5	Large mass left lung, occupying upper half mediastinum on left	Large mass receded under treatment	No biopsy. Autopsy: small bilat. mediastinal tumor; upper lobe left lung, extensive scar tissue replacement	Left pleural cavity obliterated by extensive fibrous tissue. Microscopic study: fibrous tissue infiltrated by tumor cells

TABLE 2.—SYNOPSIS OF HEMOGLOBIN AND RETICULOCYTE PERCENTAGES AND MODIFICATIONS OF IRON THERAPY IN 10 CASES OF HYPOCHROMIC ANEMIA.

Consecutive periods.	Days.	Case 1.		Case 2.		Case 3.		Case 4.		Case 5.		Case 6.		Case 7.		Case 8.		Case 9.		Case 10.	
		Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.	Hgb.	Retics.
Control	0	42	5.9	50	1.0	49	11.7	51	0.7	54	4.2	38	4.2	32	1.1	44	...	65	1.5	36	0.5
	2	43	3.6	54	5.9	52	6.3	51	1.2	59	3.3	40	2.6	32	0.7	47	2.5	65	1.1	35	1.8
	4	47	2.9	53	5.5	53	2.6	51	1.1	58	4.3	41	3.7	32	0.8	50	0.7	65	1.4	34	1.5
	6	47	2.8	59	3.9	58	3.9	..	...	57	2.7	..	...	32	1.0	47	0.7	64	1.1		
	8	45	2.2	57	2.2	60	6.3	..	...	59	2.1	..	...	33	0.9	46	0.5	63	1.3		
	10	42	1.4	56	1.6	59	3.6	..	...	58	2.1	..	...	33	0.6	43	0.5	63	1.7		
	12	..	...	54	1.0	61	2.2	..	...	59	1.8	..	...	33	0.8	41	0.7	62	0.8		
	14	..	...	54	1.0	64	1.9	..	...	56	2.2	..	...	33	0.9	42	0.4	66	0.6		
	16	..	...	..	...	64	2.2	..	...	58	2.0	..	...	33	1.8						
		Iron and ammonium citrate, 0.3 gm., mixed with mucin, 1.2 gm. t.i.d.		Iron and ammonium citrate, 0.3 gm., mixed with mucin, 1.2 gm. t.i.d.		Ferrous sulphate, 0.065 gm., mixed with mucin, 1.8 gm. t.i.d.		Ferrous sulphate, 0.062 gm., mixed with mucin, 1.7 gm. t.i.d.		Ferrous sulphate, 0.084 gm., mixed with mucin, 1.5 gm. t.i.d		Ferrous sulphate, 0.08 gm., given immediately after mucin, 4.5 gm. t.i.d.		Ferrous sulphate, 0.09 gm., given immediately after mucin, 4.5 gm. t.i.d.		Ferrous sulphate, 0.10 gm., given 1 hour after mucin, 1.7 gm. t.i.d.		Iron and ammonium citrate, 0.28 gm., mixed with 150 cc. 40% cream, t.i.d.		Ferrous sulphate, 0.08 gm., mixed with 150 cc. 40% cream, t.i.d.	
First observation	2	39	2.2	55	2.7	63	3.8	47	0.9	60	2.3	41	5.1	33	3.7	44	3.6	62	0.9	34	3.8
	4	43	2.4	58	6.5	64	3.3	51	1.9	59	2.0	41	11.7	36	5.7	45	3.9	62	2.0	38	6.3
	6	46	3.1	61	6.2	60	3.7	50	1.1	59	1.7	42	8.7	35	4.2	50	7.4	64	3.5	42	5.3
	8	48	2.3	62	4.0	63	3.6	51	1.3	60	3.2	43	8.1	36	2.7	50	10.1	66	2.4	42	3.4
	10	49	2.3	64	5.7	64	2.7	52	0.8	62	1.7	45	8.1	38	3.8	51	11.3	65	1.6	40	2.6
	12	..	...	..	...	65	2.7	53	1.2	63	1.5	45	3.4	41	4.1	56	6.1	64	1.6		
	14	..	...	..	...	..	...	..	...	..	...	46	3.0	..	...	60	5.3				
		Iron and ammonium citrate, 0.1 gm. t.i.d.		Iron and ammonium citrate, 0.3 gm. t.i.d.		Ferrous sulphate, 0.045 gm. t.i.d.		Ferrous sulphate, 0.05 gm. t.i.d.		Ferrous sulphate, 0.09 gm. t.i.d.		Ferrous sulphate, 0.09 gm. t.i.d.		Ferrous sulphate, 0.09 gm. t.i.d.		Ferrous sulphate, 0.10 gm. t.i.d.		Iron and ammonium citrate, 0.28 gm. t.i.d.		Ferrous sulphate, 0.08 gm. t.i.d.	
Second observation	2	50	3.8	66	6.7	66	2.2	55	3.2	64	1.6	46	2.2	42	1.9	60	5.5	65	2.1	42	2.8
	4	53	4.3	70	8.1	67	2.0	59	3.2	65	2.7	47	5.8	44	1.5	60	6.4	65	0.8	45	2.4
	6	58	3.2	76	6.1	70	1.9	58	1.8	65	2.0	48	10.0	47	1.5	61	4.6	65	1.8	45	2.2
	8	62	3.0	74	4.6	75	1.5	59	1.8	70	2.9	55	8.6	47	1.1	63	2.1	67	1.8	44	3.6
	10	62	2.9	80	2.8	78	1.1	60	1.1	..	...	52	3.5	48	0.7	66	1.9	68	0.9	44	3.5
	12	61	2.3	..	...	78	1.4	60	0.9	..	...	60	3.2	51	1.2	71	1.4	67	0.9	47	1.1
	14	61	0.8	..	...	..	...	59	1.3	..	...	60	2.3	54	2.5	74	1.2	..	...	47	1.6
	16	64	1.4	..	...	..	...	..	...	..	...	60	1.4	59	2.0	..	...	..	...	47	3.0
	18	66	2.8	..	...	..	...	..	...	..	...	60	2.1							48	3.6
	20																				
						Ferrous sulphate, 0.25 gm. t.i.d.		Ferrous sulphate, 0.25 gm. t.i.d.								Ferrous sulphate, 0.25 gm. t.i.d.		Ferrous sulphate, 0.25 gm. t.i.d.			
Third observation	2	..	...	..	...	78	1.6	57	3.2	..	...	..	...	..	...	77	1.4	64	1.3		
	4	..	...	..	...	80	1.3	59	3.2	..	...	..	...	..	...	78	0.9	64	0.7		
	6	..	...	..	...	80	1.4	63	5.1	..	...	..	...	..	...	76	...	66	0.5		
	8	..	...	..	...	..	...	68	4.5	..	...	..	...	..	...	80	...	70	0.3		
	10	..	...	..	...	..	...	65	3.3												
	12	..	...	..	...	..	...	65	3.2												

a second consecutive period of about 10 days either a more rapid hemoglobin increase, a second reticulocyte response, or both followed the administration of iron without mucin. A principle is thus employed which has been used to test the therapeutic effectiveness of hemopoietic substances. Minot and Castle[4] have described the method in detail. In Case 2, for example, iron and ammonium citrate, 0.3 gm., mixed with mucin, 1.2 gm., was administered 3

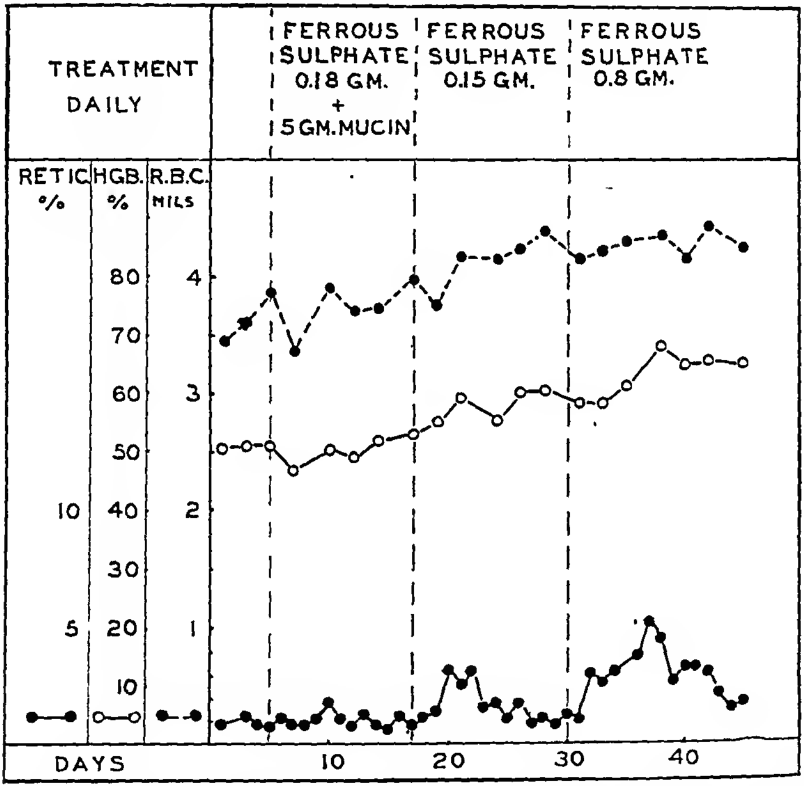

FIG. 1.—Case 4 (Tables 1 and 2). The inhibiting influence of mucin upon the utilization of iron as shown chiefly by the comparative reticulocyte responses. A negligible reticulocyte response followed the administration of ferrous sulphate mixed with mucin; a definite reticulocyte response followed the omission of mucin; an even greater reticulocyte response followed the administration of an optimal dose of ferrous sulphate.

times daily. There followed a hemoglobin increase of about 8%. A reticulocyte response occurred with a peak of 6.5% on the fourth day. On the tenth day the mucin was stopped and treatment with iron and ammonium citrate, 0.3 gm., 3 times daily was continued. During this second period the hemoglobin increased a little more rapidly (about 10% in 8 days) than during the first period, and there was a second reticulocyte response with a peak of 8.1% on the fourth day. The important point is that a second reticulocyte response occurred and not that its magnitude was greater than the first. A second response when therapy is daily and continuous implies that the material given in the second period is more potent than in the first period. The conclusion may be drawn, therefore, that the iron medication was more effective in the second period than in the first, and that the mucin, which was the only variant, inhibited in some manner the influence of the iron medication in the first period. This conclusion seems warranted also in Cases 1, 3, 4, and 5. In Case 3, no second reticulocyte response occurred, but no definite hemoglobin increase followed the administration of ferrous sulphate mixed with mucin, whereas a very definite hemoglobin increase followed the administration of ferrous sulphate alone. One must be cautious in comparing hemoglobin rises in two equal consecutive periods during iron administration. Since the hemoglobin does not usually begin to increase until several days after iron therapy has commenced, the total hemoglobin rise during the first period may not be as great as during the second period, when the effectiveness of the iron may be the same in each period. Furthermore, there tends to be a slower rate of hemoglobin manufacture as the hemoglobin level rises.

The doses of iron given were purposely small, and much less than the optimal amount to be used in the routine treatment of chronic hypochromic anemia. It is likely that if large doses of iron had been given, no inhibiting effect of mucin would have been demonstrable. In a third observation in Case 4 (Fig. 1) an optimal dose of ferrous sulphate was followed by a third reticulocyte peak, even higher than the preceding two. This merely indicates that ferrous sulphate 0.25 gm., given 3 times daily, was more effective than one-fifth this dose, which was suboptimal in this particular case.

When ferrous sulphate was given to patients separate from, but immediately after, mucin the effect was variable. In Case 6 there was a second reticulocyte response and a faster hemoglobin increase when ferrous sulphate was given without mucin, indicating that in the first period the mucin had inhibited the utilization of iron. In Case 7, there was no second reticulocyte response and no very definite increased formation of hemoglobin, so that there was no evidence that the mucin inhibited the utilization of iron in this particular case. In Case 8, ferrous sulphate was administered one hour after mucin. No increased hemoglobin formation and no second reticulocyte response occurred. One additional case (not recorded in Table 2) was given ferrous sulphate $\frac{1}{2}$ hour after mucin, and then after 10 days ferrous sulphate alone was administered, with results similar to those obtained for Case 8. The data are not included in Table 2 because there had been continuous occult blood in the stools and it was felt that this rendered the reticulocyte data doubtful. This observation serves as a control to the others, and confirms our impression that *mucin, when mixed with iron in certain doses, will interfere with the absorption of the iron in the gastro-intestinal tract.*

Cases 9 and 10 serve as an additional control to the preceding observations. In these cases, iron was mixed with a large amount of cream and administered 3 times daily. The cream had no inhibiting effect on the utilization of iron as shown by the absence of second reticulocyte responses and of increased hemoglobin formation. The figures for the hemoglobin and reticulocytes are those which would be anticipated if iron had been daily without cream.

Comment. It cannot be proven definitely from these observations that an excess secretion of mucin in the gastro-intestinal tract will materially influence the absorption of iron. In the presence of achlorhydria, however, increased amounts of mucus in the gastric contents may play some rôle in the malabsorption of iron of the food, especially when the food is deficient in available iron. There is evidence that in cases of "idiopathic" hypochromic anemia with achlorhydria the response of the blood to iron is less marked than in cases of hypochromic anemia with normal acidity of the gastric contents. Excess mucus, which may accompany low acidity, is possibly a factor in this phenomenon.

The observation that cream apparently will not inhibit the utilization of small amounts of iron given by mouth, could possibly be duplicated by the study of other food substances: carbohydrates, protein substances, bulky foods. It is common knowledge, however, that in the routine treatment of patients, iron as well as many other sorts of medication may be tolerated better if administered after meals than before meals. Food may therefore delay or prolong the absorption of certain substances if not actually reduce the amount which can be absorbed.

The observations serve to demonstrate one of the many factors which can condition the absorption of iron and presumably other necessary food substances from the gastro-intestinal tract. The problem of absorption is extremely complicated, and the list of possible factors influencing absorption in the intestine is constantly growing.[3]

Conclusion. When iron in small doses is administered with relatively large amounts of mucin to cases of chronic hypochromic anemia (iron deficiency), its absorption from the intestine is inhibited.

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CLINICAL OBSERVATIONS ON THE WHIPPLE LIVER FRACTION (SECONDARY ANEMIA FRACTION).

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In 1930, Whipple, Robscheit-Robbins and Walden[21] reported a liver fraction which was potent in the treatment of experimental post-hemorrhagic anemia. Their experiments were performed upon carefully standardized dogs in which a chronic anemia had been produced by repeated bleeding. During the past 3 years the effect of this fraction of liver has been studied at the hospital of this institute in 11 patients with chronic hypochromic microcytic anemia.

The fraction is the dry, insoluble material obtained from the precipitation of an acidified aqueous extract of whole liver with 70% alcohol. It represents 3% by weight of the whole liver or 10% by weight of the dried liver. The fraction was found by Whipple and associates to possess 65 to 75% of the potency of whole liver as measured by new hemoglobin production in the standard anemic dogs. They demonstrated by control experiments with iron feeding, that the iron content of the liver fraction was not wholly responsible for the hemoglobin regeneration in these dogs. This fraction of liver has been shown to be practically inert in the treatment of patients with pernicious anemia,[3] and conversely the fraction of liver soluble in 70% alcohol (Fraction G of Cohn), containing the hematopoietic principle effective in pernicious anemia, possesses only 10 to 20% of the potency of whole liver in the treatment of Whipple's anemic dogs[17] and exerts little or no therapeutic action in the secondary anemias of man.[10,14]

Although the oral administration of whole liver and crude extracts of whole liver has proved useful in the treatment of human secondary anemias,[5,8,9,11,14,18,19] there have been few studies of the clinical effect of Whipple's fraction of liver (Eli Lilly and Company's, Liver Extract No. 55 with Iron); in this commercial preparation 0.5 gm. of iron and ammonium citrate (83 mg. iron as metal) has been added to each 3 gm. of the dry powder (the amount of extract derived from 100 gm. of whole liver). In 1932, Cheney and Niemand[2] published a series of 50 cases of secondary anemia treated with the commercial preparation. Excellent results were obtained in 13 cases of post-hemorrhagic anemia with rises in reticulocyte, hemoglobin and erythrocyte levels, whereas other forms of secondary anemia were not strikingly benefited. Since the patients of this series received 230 to 700 mg. of iron as metal daily mixed in with the liver extract, it is impossible to evaluate the efficacy of the liver extract apart from its iron content in these cases, even though the authors reported that 6 of their post-hemorrhagic cases had failed to show material improvement on previous iron therapy. More recently Cheyney[1] has found the same commercial preparation of value in the treatment of certain cases of anemia secondary to gastric cancer.

In the course of their study of hookworm in Puerto Rico, Rhoads, Castle, Payne and Lawson[16] treated 7 patients with the No. 55 fraction without iron. On a daily dosage of 12 gm. of the extract 4 of the patients showed reticulocyte rises of from 3.6 to 13.4% followed by moderate improvement in hemoglobin and erythrocyte levels. The 12-gm. daily dose of the liver extract was found on analysis to contain 34 mg. of iron as metal which might be sufficient to exert some hematopoietic effect and thereby account at least in part for the apparent activity of the material. In all 7 cases secondary reticulocyte responses and more rapid improvement in hemoglobin and levels of erythrocytes followed the addition of 2 gm. of ferric ammonium citrate to the daily dose of liver extract.

The lack of conclusive proof that the clinical effect of the Whipple liver fraction is not entire due to the iron content stimulated the present clinical study. Heath[7] has stressed the individual variability in the iron requirement of patients with hypochromic microcytic anemia, pointing to one case which gave a maximal response to 85 mg. of iron a day by oral administration in contrast to 3 cases which showed no response whatsoever to a dose of 50 to 85 mg. per day given by the same route. Reimann and Fritsch[15] have reported good results with as little as 22 to 100 mg. of iron a day administered by mouth. It was in order to control the iron effect that the following method of procedure was adopted in the investigation of the clinical activity of the Whipple liver fraction.

Methods. Liver Extract No. 55, which was supplied without added iron by Eli Lilly and Company, was analyzed for its iron content by the method of Wong.[22] Several determinations revealed an iron content of 2.5 to 2.75 mg. of iron per gm. of dry powder, or 62 to 69 mg. of iron per 25-gm. dose of the extract.*

The principle of the double reticulocyte response was then employed in the study of the patients. This principle was introduced by Minot and his associates[11] to determine the optimal dosage of liver in pernicious anemia. Later Dameshek and Castle[4] used the method for assaying the relative potency of commercial liver extracts in the treatment of pernicious anemia, while Heath[7] has devised a similar comparative test for evaluating the efficacy of various iron preparations in the treatment of hypochromic anemia. As stated by Dameshek and Castle, the principle of the double reticulocyte response is briefly this: When a uniform daily suboptimal dose of a known potent material is given, the reticulocyte response is concluded or on its downward course in from 10 to 12 days. This allows for the observation of a possible second response of reticulocytes when another more potent material or a larger dose of the same material is given over a period immediately following the first period. Daily doses must be used since the stimulus to the bone marrow must be continuously applied during the estimation of the comparative potency of each product.

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* We are indebted to Dr. Walther Goebel for the information that the iron in the liver fraction is chiefly in the ferrous state, although a small portion is ferric iron.

Applying this principle of the double reticulocyte response, we have treated patients with severe hypochromic microcytic anemia continuously over 3 consecutive periods of at least 10 days each. In the first period, each patient received about 70 mg. of iron a day as 1.7 cc. of a 25% solution of ferric ammonium citrate, in the second period 25 gm. of Liver Extract No. 55 (the amount derived from 833 gm. of whole liver) daily, and in the third period a maximal dose of inorganic iron preparation. Reticulocytes were followed throughout the first two periods in all cases, and through the third period in the majority of the cases. We have felt that after giving 70 mg. of iron a day throughout the first period we were justified in interpreting any further reticulocyte response occurring in the second period as due to some factor or factors in the liver fraction other than the contained iron. In other words, we have looked upon the first period as controlling the iron content of the liver fraction.

TABLE 1.—RETICULOCYTE PEAK OBTAINED WITH SMALL DOSES OF IRON, LIVER EXTRACT AND LARGE DOSES OF IRON.

Patient.	Sex.	Age.	Diagnosis.	Blood picture at start of test period.					Reticulocyte peak (%).		
				R.B.C. (in millions).	Hemoglobin (%).	M.C.V. (μ^3).	C.I.	Reticulocytes (%).	I. 70 mg. iron q.d.	II. L.E. No. 55 $\bar{s}$ iron, 25 gm. q.d.	III. Large dose of iron q.d.
1. F. P.	M	41	Ulc. colitis	4.05	37	58	0.46	0 8	1.6	4.0	11.2
2. H. B.	M	21	Ulc. colitis	3.18	46	73	0.72	1.4	6.0	12.5	
3. A. Z.	F	27	Ulc. colitis	2.61	30	69	0 58	2.0	7.0	6.8	12.1
4. E. T.	M	20	Banti's disease Hematemesis	4.60	56	61	0 61	1.8	4.2	5.6	
5. O. L.	F	45	Ca. of small intestine	2.43	41	78	0 84	0.6	4.0	9.8	9.0
6. E. W.	F	58	Ca. of cecum Achlorhydria	4.14	45	59	0.54	1.8	4.5	3.9	5.7
7. M. M.	F	29	Myomata uteri	3.82	51	68	0.67	0.4	2.4	15.8	8.0
8. M. B.	F	47	Gastro-enterostomy Hypochlorhydria	3.40	40	65	0.58	0.4	1.2	3.0	
9. C. L.	F	55	Hypochlorhydria	2.74	34	62	0.62	1.8	4.8	5.2	
10. H. P.	F	70	Nutritional anemia	3.31	43	70	0.65	1.2	5.4	5.2	3.0
11. L. B.	M	64	? Ca. of prostate; metastasis to bone	3 00	39	68	0.65	0.2	3.0	4 2	4 4
Average				3.39	42	66	0.63	1.2	4.0	6.9	7.6

Case Material. Eleven cases of severe hypochromic anemia (Table 1) were studied in the manner just described: 7 patients were females; 4 males. The ages varied from 20 to 70 years. Chronic blood loss was regarded as the chief etiologic factor in the first 7 patients, 3 of whom were suffering from chronic ulcerative colitis. Gross blood loss of sufficient magnitude to stimulate a reticulocyte response was not observed in any of these 7 patients during the period of observation. Cases 8 and 9 showed gastric hypochlorhydria, associated with a gastro-enterostomy in Case 8. Case 10 presented the typical picture of nutritonal anemia resulting from an inadequate iron intake over a period of years, while Case 11 was a man with carcinoma (probably of the prostate) with multiple metastases to bone.

The original erythrocyte levels of the 11 patients varied from 2,430,000 to 4,600,000 red blood cells per c.mm., while the hemoglobin levels ranged from 30 to 56%. In 9 cases the hemoglobin level was below 50%. The mean corpuscular volume and color index were well below normal in all

11 cases, averaging 66 μ^3 and 0.63 respectively. The reticulocyte levels at the start of the observation period varied from 0.2 to 2%. Thus these 11 patients all satisfied the usual criteria of hypochromic microcytic anemia with reticulocytes stabilized at a low level when the therapeutic tests were started.

Results. Eight of the 11 patients showed at least a slight reticulocyte response to the oral administration of 70 mg. of iron a day during the control period. These responses varied from 1.2 to 7% and occurred between the fourth and tenth day after the initial dose of iron. Following the peak, the reticulocyte curve either declined or flattened out until 25 gm. of Liver Extract No. 55 daily were substituted for the inorganic iron preparation in the second observation period. Then each of the 11 cases gave a secondary reticulocyte response to this liver fraction, the peak of the rise ranging from 3 to 15.8%. A moderate rise in levels of erythrocytes and hemoglobin occurred during these first two periods of therapy; however, the rate of improvement in blood levels was much more rapid in the third period when the patients were receiving large doses of inorganic iron. Of the 7 cases where reticulocytes were followed throughout the third period 5 developed tertiary reticulocyte rises which equalled or excelled the primary and secondary responses. Examples of the blood changes taking place during the three consecutive test periods are presented in Figures 1 to 6, while Figure 7 and Table 1 summarize the data for the entire series of 11 cases.

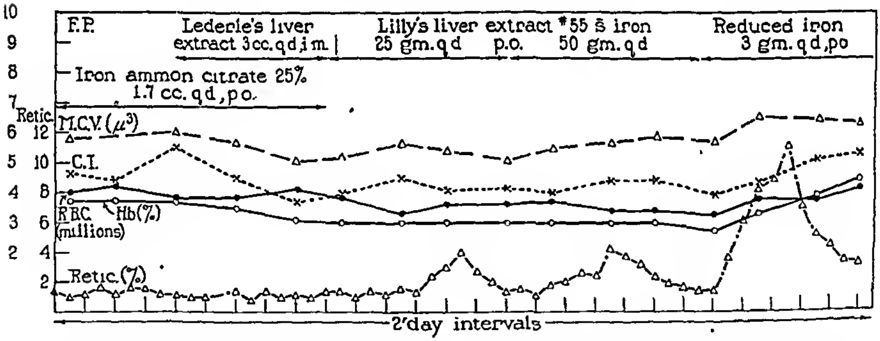

FIG. 1.—Case 1. F. P., male, aged 41. Chronic ulcerative colitis. No reticulocyte response to 70 mg. of iron a day or to antipernicious anemia liver fraction. Slight reticulocyte response to "secondary anemia" liver fraction and excellent response to large doses of reduced iron.

Discussion. It is quite apparent from examination of Table 1 and the text figures that all 11 cases of hypochromic microcytic anemia showed at least slight secondary reticulocyte responses to the No. 55 liver extract, which averaged 2.9% higher than the original response to the 70-mg. dose of iron. These figures suggest that the secondary anemia liver extract contains clinically active hematopoietic material apart from its iron content. The nature of this material is not known. Patek and Minot[13] have described reticulocyte responses to the oral adminstration of bile pigment following a period of iron medication in cases of hypochromic microcytic anemia, and Patek[12] has reported similar reactions to the administraton of chlorophyll

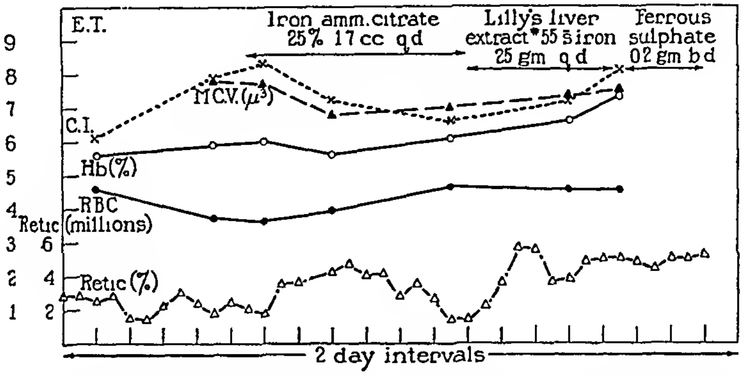

FIG. 2.—Case 4. E. T., male, aged 20. Banti's disease. Large hemorrhage 3 weeks before admission. Reticulocyte rise to 4.2% during control period; secondary rise to 5.6% during liver extract period.

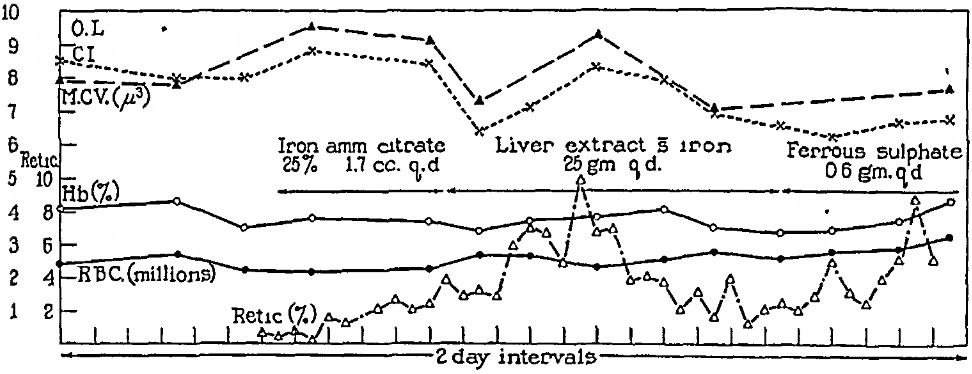

FIG. 3.—Case 5. O. L., female, aged 45. Carcinoma of small intestine. Reticulocyte rise to 4% during iron control period; further rise to 9.8% during liver extract period; tertiary response of 9% to 0.6 gm. of ferrous sulphate daily.

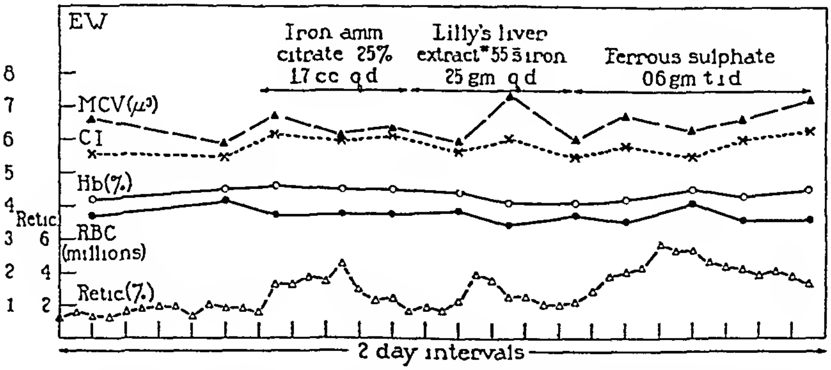

FIG. 4.—Case 6. E. W., female, aged 58. Carcinoma of cecum, histamine achlorhydria. Slight reticulocyte rises in each of the three consecutive observation periods without appreciable improvement in erythrocyte or hemoglobin levels.

products following a suboptimal dosage of iron. These observations have been interpreted as evidence that the human body may utilize the pyrrols present in bile pigment and in chlorophyll for the formation of new hemoglobin. As early as 1925 Whipple and Robscheit-Robbins[20] concluded that parent pigment substances are stored in the normal liver. It may be that the No. 55 liver fraction supplies such parent pigment substances for new hemoglobin formation. On the other hand, it is conceivable that this liver fraction may improve the absorption or utilization of iron.

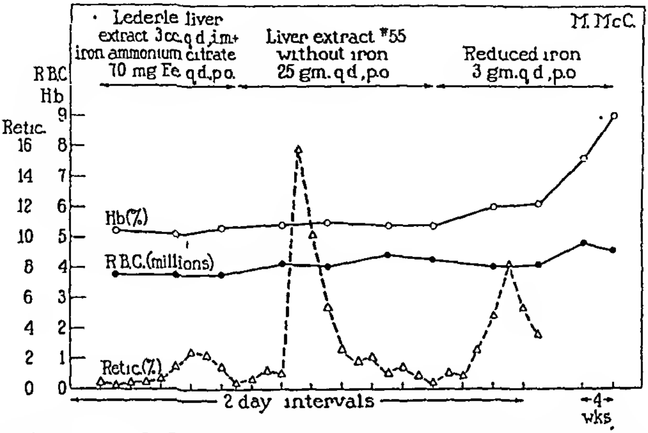

FIG. 5.—Case 7. M. McC., female, aged 29. Myomata uteri with previous hemorrhage. No blood loss during test period. Slight reticulocyte response to 70 mg. of iron a day; sharp secondary reticulocyte rise to 15.8% on the liver extract; moderate tertiary response to reduced iron in large dosage followed by rapid rise in hemoglobin.

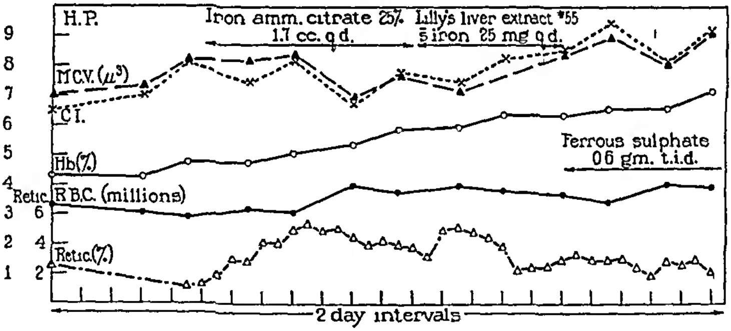

FIG. 6.—Case 10. H. P., female, aged 70. Nutritional anemia. Reticulocyte response of 5.4% to 70 mg. of iron and secondary response of 5.2% to the liver fraction. Steady rise in hemoglobin level.

In view of the fact that the iron contained in the liver fraction is chiefly ferrous iron whereas ferric iron was administered in the control period, it is possible that the secondary reticulocyte rise may be attributed to the recognized superiority of ferrous over ferric iron in the treatment of hyperchromic anemia. How much of the iron contained in the liver fraction is available and absorbed is not known.

Hart *et al.*[6] have shown that the effect of whole liver or liver extracts on nutritional anemia of the rat produced by a diet of milk is directly proportional to the available content to iron and copper. The iron-copper ratio of the liver fraction used in our experiments is not known. It is possible that the iron-copper ratio was brought more nearly to normal by the administration of the liver fraction; this may be the explanation of the reticulocyte rise. Our present studies furnish no data to substantiate or disprove any one of these hypotheses as to the mechanism of action of the liver fraction.

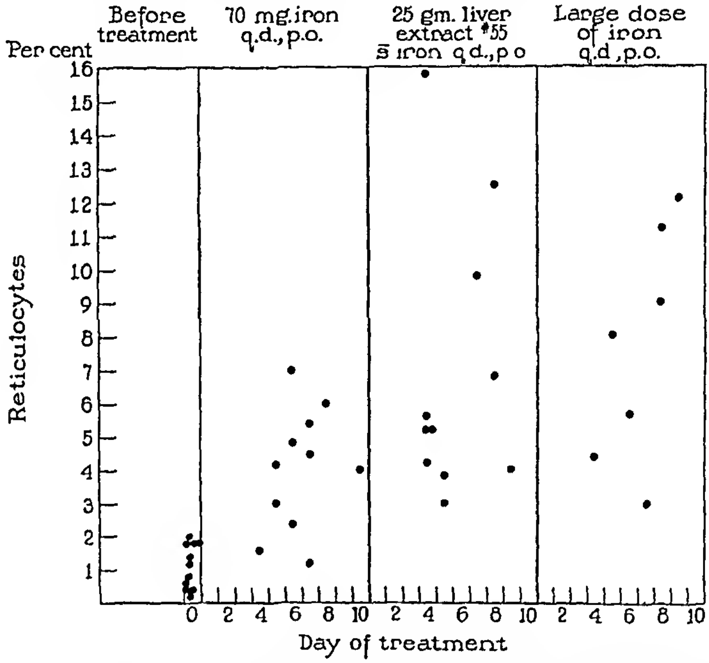

FIG. 7.—Composite chart of 11 cases. Reticulocyte peaks plotted against days on which these peaks occurred during the three consecutive observation periods.

The tertiary reticulocyte responses to maximal doses of inorganic iron and the more rapid improvement in blood levels on this form of treatment may be regarded as further evidence that iron in adequate amounts is the most effective therapeutic agent in the hypochromic microcytic anemias of man.

Summary and Conclusions. The secondary anemia liver fraction of Whipple and his coworkers has been administered orally to 11 patients with chronic hypochromic microcytic anemia. A rise in circulating reticulocytes occurred in every case.

Through the application of the principle of the double reticulocyte response to control the iron content of the liver fraction, it appears likely that the liver fraction contains reticulocytogenic material apart from its iron content.

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PULMONARY INVOLVEMENT IN LYMPHOSARCOMA AND LYMPHATIC LEUKEMIA.*

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We published a paper, in 1935,[3] concerning Hodgkin's disease of the lung. At that time studies were planned to include pulmonary involvement in two other members of the so-called lymphoma or lymphomatoid[5] group of diseases, lymphosarcoma and lymphatic leukemia. This report concerns our data on the latter two diseases.

The material is from patients admitted to the University of California Hospital from 1920 to 1937, inclusive. Our studies attempt to correlate the clinical, pathologic, and roentgenologic findings in those cases showing pulmonary involvement. Under pulmonary involvement, we include bronchial and hilar lymph nodes, pleura, and parenchyma of the lungs. In no case in either series is the involvement limited to bronchial and hilar lymph nodes with the possible exception of Case 10, Table 2. An autopsy could not be obtained for verification of parenchymal involvement of the lung in this case.

Table 1.

Authors.	Cases lymphosarcoma.	Pulmonary involvement.	Per cent.	Cases lymphatic leukemia.	Pulmonary involvement.	Per cent.
Kirklin and Hefke . .	84	17	20	48	10	21
Falconer and Leonard .	25	9	36	30	9	30

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* Read before the General Medicine Section of the California Medical Association at the 66th Annual Session, Del Monte, May 2 to 6, 1937.

18	M. A. F 34	24	4	Right pleural effusion	Several courses with good response at first	Cervical node tumor and rib biopsies: diag. Hodgkin's dis. Autopsy: extensive involv. throughout entire body. Fluid in both pleural sacs	Hilar and mediastinal lymph nodes involved. Pleural adhesions and nodular infiltration
19	D. R. M 60	1	1	Diffuse shadow base of left lung suggesting malignancy	Unsatisfactory response	No biopsy. Autopsy: bilat. pleural effusion, mediastinal lymph nodes enlarged	Left lung adherent to diaphragm. Diffuse pulmonary infiltration
20	L. J. J. M 68	6	8 (still under observ.)	Lymphatic infiltration stomach, chest film 12-20-36; also enlarged hilar nodes, right pleural effusion	Two courses, 1936; one, 17; one, 12 treatments	Biopsy, cervical lymph node: lymphosarcoma	Disease spread cervical region to stomach and abdomen, then chest, neck, parotid region and eyelids with Mikulicz's syndrome. Response to Roentgen therapy good
21	D. K. F 53	36	12	Right hilar nodes enlarged, lower portion right lung discrete nodules, extensive infiltration left lung with nodules	Only fair response	Biopsy cervical lymph node: lymphosarcoma. Autopsy: in right lung, large, solid mass involving upper and middle lobe. Lung tissue destroyed and replaced by fibrous tissue	Large white mass in right side of mediastinum. Multiple small nodules lower lobe. Left lung, mass upper lobe, nodules lower lobe
22	E. C. M 30	Primary	7 (still under observ.)	Pleural effusion left. Huge masses of glands in posterior mediastinum	Satisfactory response	Biopsy left axillary lymph node: lymphosarcoma	Bilateral pleural effusion. Venous obstruction upper chest and neck. Example of paratracheal node involvement
23	E. J. F 27	24	48 (still living)	Mass involving upper lobe right lung, compressing trachea	Fair response	Two biopsies cervical lymph nodes: lymphosarcoma. Upper mediastinum filled by mass, marked obstruction to breathing	Right chest filled with fluid reported to have become purulent. Patient under treatment in Germany

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* We are indebted to Drs. George Weaver of Stockton, Calif., and Sydney Shipman of San Francisco, Calif., for permission to use the data concerning Case No. 17 (G. H.).

Incidence.—Search of the literature for statistics of incidence showed surprisingly few reports. Those found are concerned for the most part with the roentgenologic aspects. Cutler[2] studied 30 patients with lymphosarcoma, 13 of whom came to autopsy. His statistics of pulmonary involvement are listed under separate headings—mediastinum, pleura, and parenchyma of the lung. Nine showed involvement of mediastinum; 7, pleura; and 3, parenchyma of the lung. Two recent papers dealing with the roentgenologic aspects of Hodgkin's disease and lymphosarcoma, are those of Williams,[9] and Pierce, Jacox, and Hildreth.[7] Not all of the cases in the respective series of these authors are proven by biopsy. Kirklin and Hefke[4] have reported an interesting study, from the roentgenologic aspects, of Hodgkin's disease, lymphosarcoma and lymphatic leukemia. These studies were made upon patients at the Mayo Clinic. All of their cases are proven by biopsy, with the possible exception of the lymphatic leukemia patients. Statistics of the Kirklin and Hefke series appear below and show a lower incidence of pulmonary involvement than our statistics. This applies to both lymphatic leukemia and lymphosarcoma, and is readily explained by the fact that Kirklin and Hefke's patients were under observation for relatively short periods and autopsy findings were not available in the majority of cases.

The true incidence of pulmonary involvement must rest largely on statistics based upon postmortem examination from the very nature of the two diseases. Beginning as local processes, both diseases spread throughout the body, until at autopsy there is wide dissemination. Exceptions to this usual course of development are occasional cases, in both disease groups, where the process remains relatively localized.

In our patients with lymphosarcoma where the process has been localized to the more superficial groups of lymph nodes, Roentgen films of the chest have been negative. Our observations in the lymphatic leukemia group are too few to permit of any conclusion.

Pathologic Anatomy. In contradistinction to the findings in Hodgkin's disease (Moolten[6]), primary involvement of pulmonary parenchyma in lymphosarcoma and lymphatic leukemia must be rare. We found no reference to this particular phase of study in the literature. No cases were found in our present study where clinical and pathologic evidence suggested inception of the disease in the parenchyma of the lung. Bernard[1] considers primary pleural involvement in Hodgkin's disease more common than primary manifestation in the parenchyma of the lung. This accords with our observations in the two diseases of the present study. The term "primary pleural involvement," is used here in a rather loose manner, as it is exceedingly difficult, if not impossible, in a given case to discover where lymphatic leukemia or lymphosarcoma has its earliest inception, just as it is often quite impossible to say where the initial

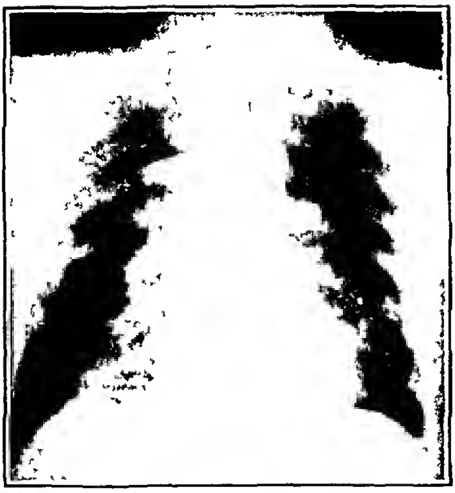

FIG. 1

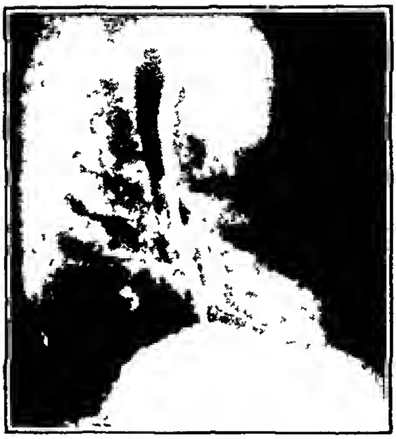

FIG. 2

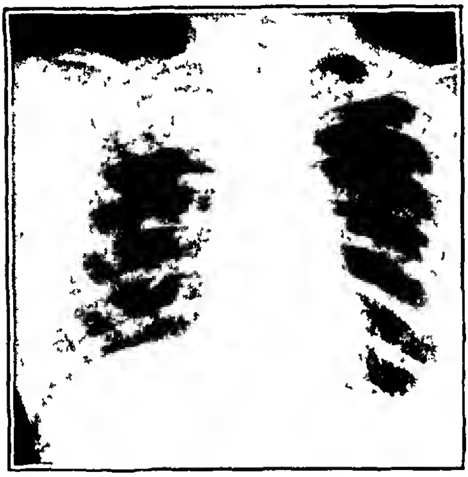

FIG. 3

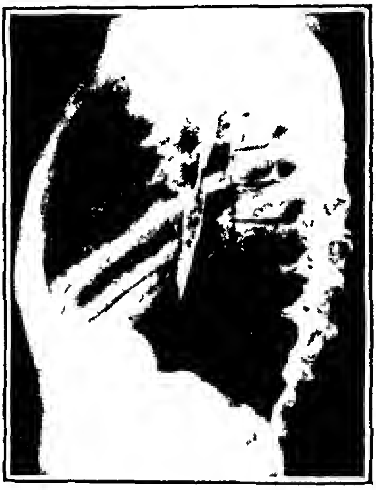

FIG. 4

FIGS. 1 and 2, lymphatic leukemia; contrast with Figs. 3 and 4, lymphosarcoma. Note left paratracheal node involvement in both patients. Fig. 1 is almost identical with Fig. 3 of Williams' article, Fig. 4 illustrating "typical" paratracheal node involvement characteristic of Hodgkin's disease. Lateral views illustrate why these patients had marked venous compression. (Patients 10 and 23, Tables 2 and 3.) Barium in esophagus.

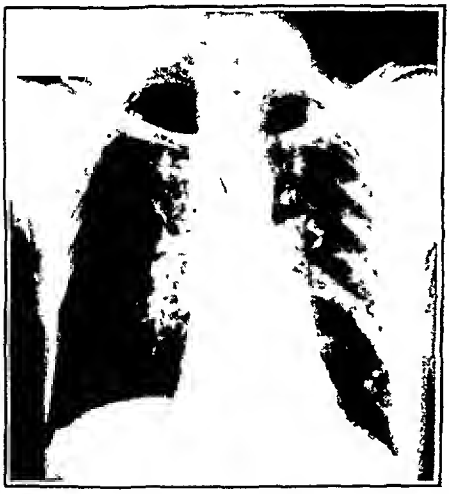

FIG. 5

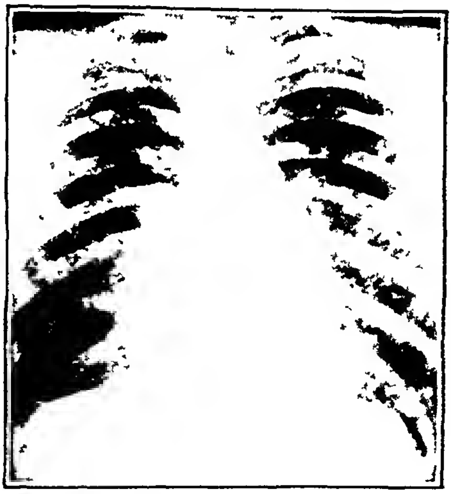

FIG. 6

FIG. 5, lymphatic leukemia; FIG. 6, lymphosarcoma. Illustrative of miliary type of distribution of pulmonary lesions. Responded to Roentgen therapy by rapid clearing of lungs, but progress of disease in both instances unchecked. (Patients 3 and 16, Tables 2 and 3.)

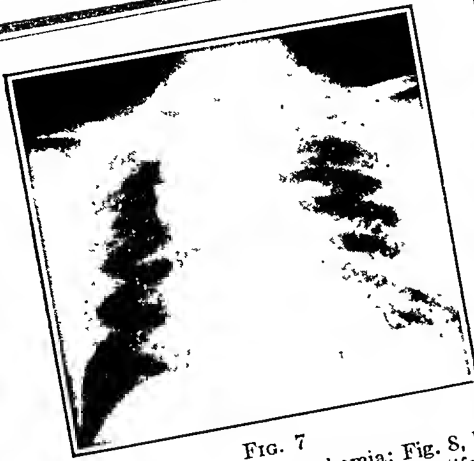

Fig. 7

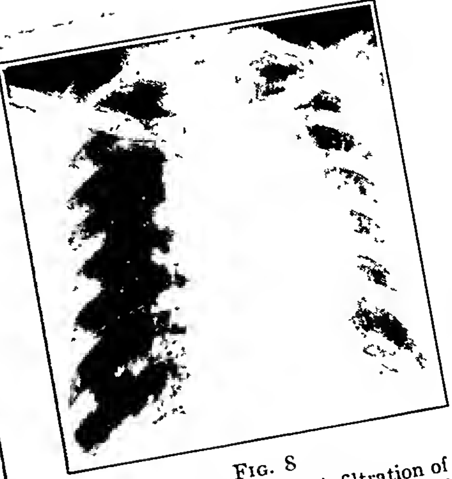

Fig. 8

Fig. 7, lymphatic leukemia; Fig. 8, lymphosarcoma. Note massive infiltration of lung parenchyma. Fig. 7 shows "feathering out" appearance at left margin of tumor, supposed to be characteristic of Hodgkin's disease. Pulmonary lesions receded under Roentgen therapy. Tumor tissue at autopsy found replaced by extensive fibrosis. Fig. 8, diagnosed originally as bronchogenic carcinoma from Roentgen films and bronchoscopy. (Patients 8 and 17, Tables 2 and 3.)

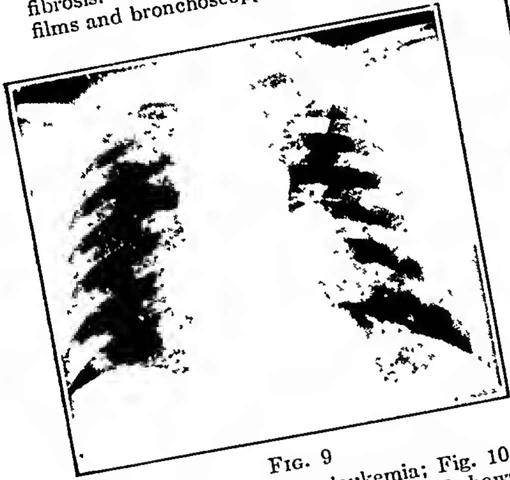

Fig. 9

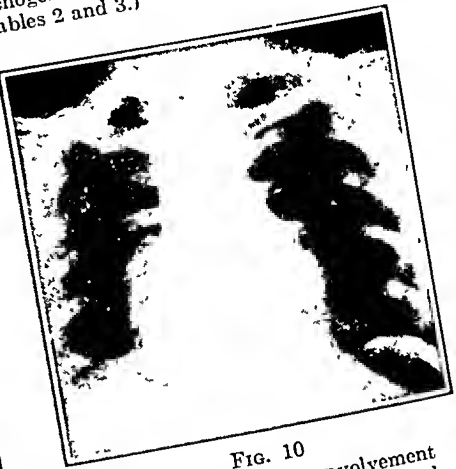

Fig. 10

Fig. 9, lymphatic leukemia; Fig. 10, lymphosarcoma. Hilus node involvement very similar in each case. Fig. 10 shows a small pleural effusion, right, which cleared rapidly under Roentgen therapy. (Patients 7 and 20, Tables 2 and 3.)

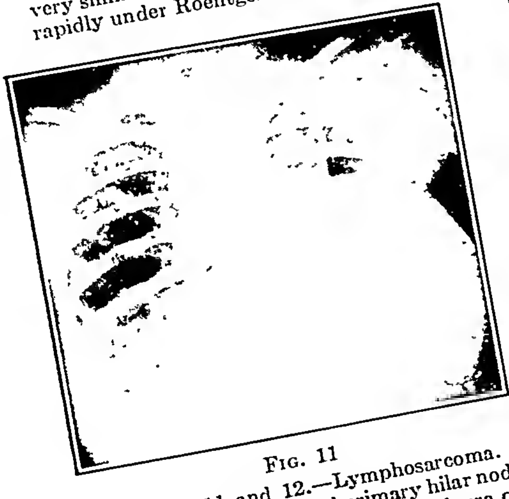

Fig. 11

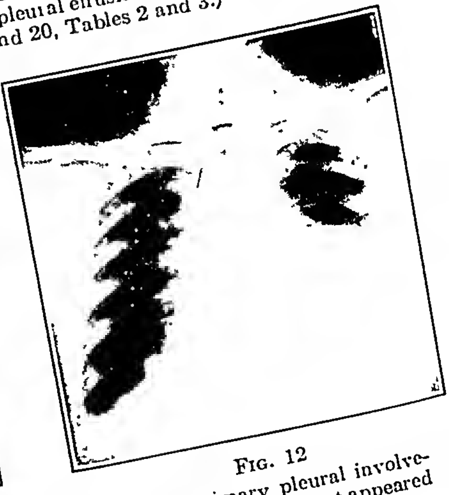

Fig. 12

Figs. 11 and 12.—Lymphosarcoma. Fig. 11 probably primary pleural involvement. Fig. 12 showed primary hilar node involvement; pleural involvement appeared early. Fig. 11, note thickened pleura on left after introduction of air in pleural sac. (Patients 11 and 22. Table 3.)

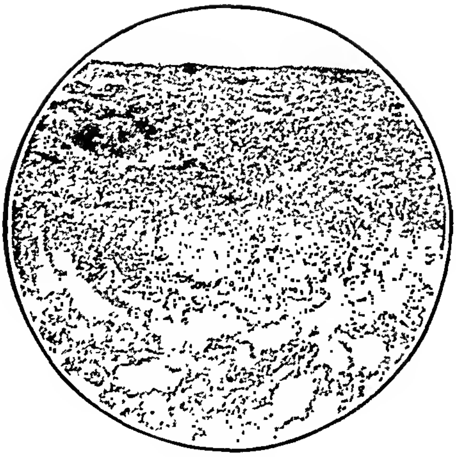

Fig. 13

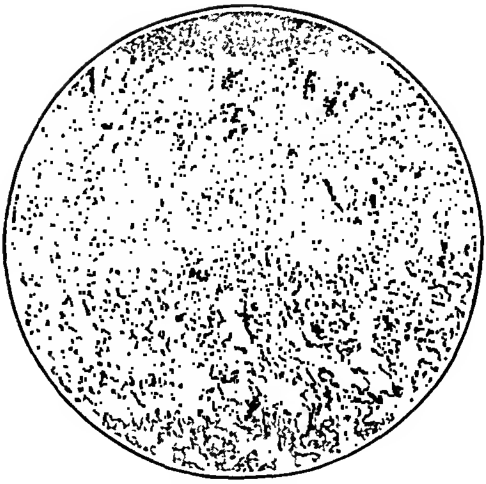

Fig. 14

Figs. 13 and 14.—Lymphatic leukemia, and lymphosarcoma. Sections through pleura, showing normal lung tissue beneath. Note similar, remarkable, fibrous thickening of pleura in both cases. Extensive tumor cell infiltration. (Cases 11 and 12, Tables 2 and 3.) Probably primary pleural involvement.

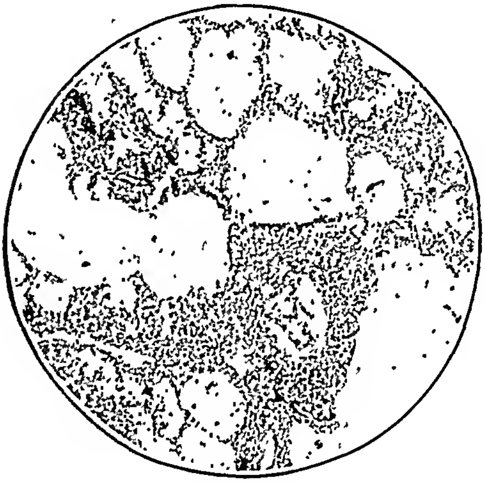

Fig. 15

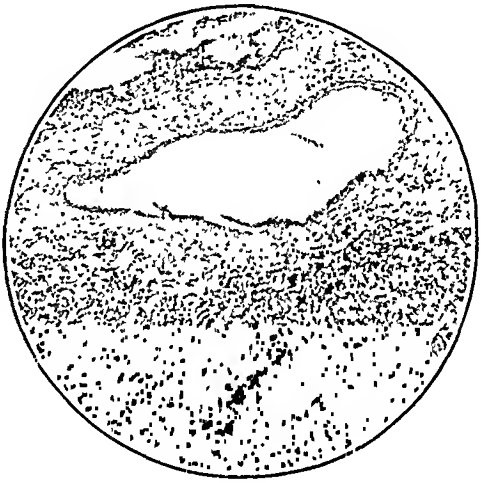

Fig. 16

Figs. 15 and 16.—Lymphatic leukemia, and lymphosarcoma. Note similarity in type of pulmonary invasion. In both figures tumor nodule shows cross-section of an artery. Note perivascular infiltration. (Cases 6 and 15, Tables 2 and 3.)

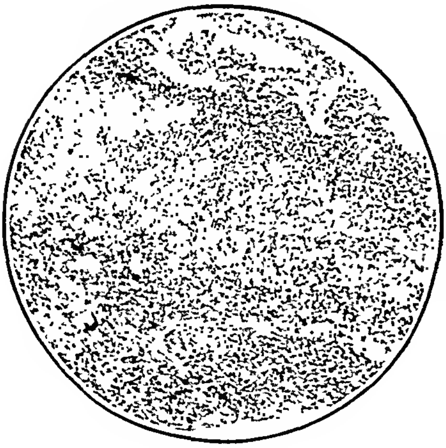

Fig. 17

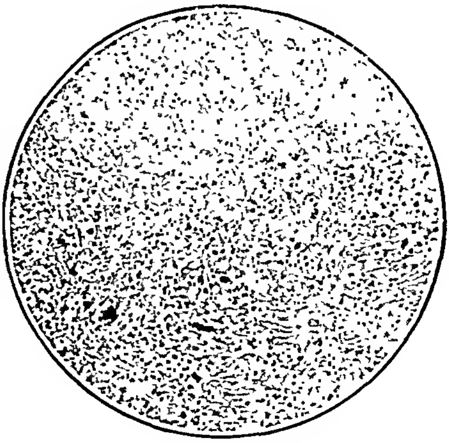

Fig. 18

Fig. 17.—Details of leukemic infiltration of pleura. Note uniformity of cells. (Case 11, Table 3.)

Fig. 18.—Extensive invasion of lung tissue by lymphosarcoma. Note pleomorphism of cells, also replacement of tumor by connective tissue. (Case 21, Table 3.)

lesion of pulmonary tuberculosis is located. In this connection, however, it is interesting that in Cases 11 (Table 2) and 12 (Table 3) (lymphatic leukemia and lymphosarcoma) the involvement was apparently first pleural, then in the hilar lymph nodes, a situation comparable to what supposedly occurs in certain cases of pulmonary tuberculosis. Case 22 (Table 3) showed the first clinical signs of his disease (lymphosarcoma) in the mediastinum and pleura. As this patient is still under observation, nothing definite can be said concerning the initial lesion.

In grouping our patients in both series according to type of pathologic involvement, Versé's[8] classification is used. Table 4 shows the percentage for the different types, in both series of diseases.

TABLE 4 (VERSÉ).—SEPARATION INTO 5 TYPES ACCORDING TO LOCATION OF LUNG INVOLVEMENT.

Lymphatic leukemia.						Lymphosarcoma.					
I.	II.	III.	IV.	V.	Total.	I.	II.	III.	IV.	V.	Total.
5	1	2	2	2	12	3	3	1	0	4	11

This method of separating different types of pulmonary involvement was originally suggested for Hodgkin's disease by Versé, who described the types as follows:

"I. Hilar node involvement with direct invasion of lung tissue: (*a*) By direct extension from the lung hilus; (*b*) by breaking through the mediastinal pleura. II. Hilar node involvement with intra- and peribronchial spread into the lungs. III. More or less lobar infiltration with various grades of bronchomediastinal involvement. IV. Confluent lobular foci with associated involvement of lymph nodes. V. Miliary disseminations."

Pleural effusion was present in a high percentage of our series, in both diseases. The lymphatic leukemia group showed 64%, 7 of the 11 patients. In the lymphosarcoma group the figure was slightly higher, 67%, *i. e.*, 8 of the 12 patients in the series. Of the 7 pleural effusions in the first group, 2 were bilateral, 3 left sided, 2 right sided. The 8 cases with effusion in the lymphosarcoma group showed bilateral 5, right sided 2, left sided 1. In our series of cases of Hodgkin's disease,[3] 71% of the series (7 patients) showed pleural effusion, probably too high a percentage, owing to the small number in the series.

This high incidence of pleural effusion is striking, and stresses the importance of Roentgen films of the chest at regular intervals, particularly when signs and symptoms indicate progression of the disease. It is our impression from analysis of these series, that cases with massive pleural effusion respond unsatisfactorily to Roentgen therapy.

Patients 12 (Table 3) and 11 (Table 2) lymphosarcoma and lymphatic leukemia, are probably cases with primary pleural involvement. The earliest symptoms were referable to the chest.

Pleural effusion was found shortly after the onset of symptoms. In both instances the microscopic picture of the pleura, showing considerable fibrous tissue replacement, is indicative of early pleural involvement, particularly as the entire length of disease was only 10 and 16 weeks, respectively.

Roentgen Studies. In our studies on Hodgkin's disease,[3] we came, to the conclusion that there was no characteristic Roengten picture of pulmonary Hodgkin's disease. The same conclusion is obvious from our studies on lymphosarcoma and lymphatic leukemia. A similar opinion is expressed by Kirklin and Hefke.[4] They state that roentgenologic data at the present time do not permit of an exact differential diagnosis. To quote from their article: "Any of the three diseases may exactly resemble either of the other two, and in view of their morbid anatomy, this might be expected."

It is not within the scope of this report to discuss results of Roentgen therapy. For those interested we might state our impression, that Roentgen therapy accomplished no more than symptomatic relief in our series of patients. The cases were, with few exceptions, the less favorable types, with steady downward progression, and when pulmonary involvement occurred, the disease was well implanted in other portions of the body.

Prognosis. In the lymphatic leukemia group, the duration of life was 2 months to 11 years, 8 patients living less than 4 years after onset of symptoms. In the lymphosarcoma series the figures for duration of life are 4 months to 4½ years, 8 living less than 4 years after onset of symptoms. Pulmonary involvement in the majority of patients in both series tended to occur rather late in the course of the disease or more precisely speaking, it tended to occur when the disease became widespread in the body. Exceptions to this finding occurred and have been discussed under pleural involvement. Once the parenchyma of the lung becomes involved or pleural effusion supervenes, the outlook, both as to tenure of life and induction of remissions by Roentgen therapy, is poor. This conclusion appears warranted from our studies, but it cannot in any sense be accepted as a rule to be followed. Patients with either disease under discussion vary greatly in their sensitivity to radiation, and for this reason it should always be used to the full limits of its possibilities.

Summary. The figures for pulmonary incidence were: lymphatic leukemia, 30%; lymphosarcoma, 36%. Our findings in Hodgkin's disease showed 31%. These figures enhance in interest if one is to consider Hodgkin's disease an infection, and the former two diseases neoplastic in nature. From the clinical, roentgenologic and pathologic aspects, our studies with reference to pulmonary involvement in the 3 groups of diseases showed a striking similarity. There were, of course, some minor differences, for example, the difference in the grouping of cases under the Versé classification. However, *this grouping depends largely on individual interpretation* of the pathologic findings and will vary according to the extent and thoroughness of the microscopic study of the tissues at necropsy.

In our series of cases of Hodgkin's disease,[3] the time between onset of disease and appearance of pulmonary symptoms varied from onset with pulmonary symptoms to 8 years. In 2 patients pulmonary symptoms were primary. In the other 5 patients of the series, the time varied from 2 months to 8 years. Length of life after onset of pulmonary involvement varied from 22 months to 4 years and 3 months. These figures, when compared with the corresponding figures for lymphatic leukemia and lymphosarcoma, show that the patients of our Hodgkin's disease series apparently ran a more slowly progressive and chronic course than the cases comprising the two series of the present study. The importance *of this study, along with our study of Hodgkin's disease, is to point* out the similarity, both as to pulmonary incidence and types of involvement, in these three diseases, which are frequently included under a generic term: lymphoblastoma, lymphoma, or lymphomatoid[5] group of diseases.

We wish to thank Dr. C. L. Connor, Chief of the Department of Pathology, for his suggestions and advice. We are also indebted to Drs. Robert Stone and C. S. Capp of the Department of Roentgenology for the interpretation of the roentgenograms used in this study.

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ELECTROCARDIOGRAPHIC CHANGES AND PERIPHERAL NERVE PALSIES IN TOXIC DIPHTHERIA.

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It is our purpose to record the results of an investigation into the clinical, electrocardiographic and pathologic changes due to cardiac complications in toxic diphtheria. Peripheral nerve palsies closely parallel these complications, and data relative to their occurrence are included in this study.

In 1900, Councilman, Mallory and Pearce[2] described the tissue changes in 220 patients dying of diphtheria. Extensive histologic studies on fresh and fixed sections of the myocardium were made on 60 of them. Of this latter group, 36 showed fatty degeneration of the muscle fibers. The more advanced changes consisted of progressive necrosis leading to complete destruction of the fibers. They found little relationship between the duration of the disease and the presence of fatty degeneration. This type of degeneration was generally the only finding of great severity in the patients who died early in the disease. They found, however, a definite relationship between the intense degenerative changes (necrosis) and the duration of the diphtheritic infection.

Warthin,[8] Marvin,[4] Nathanson,[5] Strecker,[7] Alstead[1] and others described the changes found in electrocardiograms on patients suffering from toxic diphtheria. These alterations consist of depression of the *S–T* line, inversion of the *T* wave, intraventricular block and auriculoventricular dissociation.

Josephthal[3] produced electrocardiographic changes in the rabbit, analogous to the changes encountered in toxic diphtheria, by injecting sublethal doses of diphtheria toxin. The records on the rabbits showed the progressive development of negative *T* waves and intraventricular block.

Clinically, the mortality in diphtheria is credited for the most part to myocardial failure, and the average death certificate reads: contributory cause, toxic myocarditis.

Our studies attempt to correlate the cardiac changes as determined by clinical observation, serial electrocardiograms and autopsy material. These observations serve to demonstrate the pathogenesis of this complication by recording the time of onset and the progress of myocardial changes during the course of the primary diphtheritic infection.

The methods of investigation adopted comprised the taking of electrocardiograms on patients showing membranes and toxic manifestations of diphtheria. The graphs were taken soon after admission and repeated every second or third day during the course in the hospital. Tracings were taken daily or twice daily on patients showing marked changes in the contour of the electrocardiograms.

Early in the course of our studies, peripheral nerve palsies seemed to occur with unusual frequency in the patients who showed abnormalities in the electrocardiograms. Because of this fact, the date of their occurrence, in the course of the illness, was recorded to determine whether they were in any way related to the cardiac manifestations.

Although this investigation was carried on for approximately 2½ years, and included some 140 cases of toxic diphtheria, only 28 showed electrocardiographic evidence of cardiac damage. This latter group comprise the basis of the present study together with some additional pathologic material taken from the autopsy records of the hospital.

The Electrocardiographic Changes. All patients admitted early in the disease yielded normal electrocardiograms except for the presence of tachycardias. The abnormal features, which developed during the subsequent course of the disease, were divisable into the following two groups: 1, Alterations in the *T* wave; 2, alterations in the conduction system, including auriculoventricular block and intraventricular block.

The T-wave Variations. The earliest change noted, on the electrocardiogram, was a slight decline in the *S–T* line and a decreased amplitude of the *T* wave. It soon became evident that the occurrence of this change portended the development of more radical alterations. The *T* wave generally fell progressively until it became isoelectric, 1 or 2 days later it would become diphasic and subsequently inverted. The *T* wave returned to normal in the reverse order of events. This phenomenon occurred in all 3 leads, but it was most pronounced in the second lead.

Of 23 patients showing these changes, the earliest occurred on the fifth day of illness and the latest on the thirty-ninth day, with

TABLE 1.—TOXIC DIPHTHERIA CASES SHOWING ELECTROCARDIOGRAPHIC CHANGES IN THE *T* WAVE.

Case No.	Age.	Days from onset of illness to antitoxin.	Amount of antitoxin in 1000 units.	Days from onset to *T*-wave change.	Duration of *T*-wave change.	Days from onset to peripheral nerve paralysis.	Comment.
5	28	4	50	15	36	30	Normal on discharge.
7	11	4	40	15	20	10	Normal on discharge and 1 yr. later.
12	2	8	50	8	1	. . .	Died; autopsy.
16	4	6	38	24	12	27	Also conduction change 9th day.
17	19	3	82	*	*	32	Died suddenly 61st day of illness
19	33	3	40	13	7		
26	8	5	40	10	44	14	
27	7	2	40	27	6	8	
30	25	7	50	14	7		
34	18	(9) none	None	9	72	38	
37	36	7	80	21	38	45	
41	5	4	30	18	7	32	Also conduction change 8th day.
54	6	6	40	9	59	27	
69	57	6	25	14	26	35	Died; autopsy.
76	2	3	35	39	1		
77	4	(9) none	None	7	25	. . .	Ventricular escape.
78	53	5	35	8	1	16	
97	10	6	30	11	25	9	
103	24	4	45	5	13		
105	38	3	40	16	43	20	
124	26	6	50	19	19	26	
126	6	3	20	9	47	21	
127	4	4	30	10	38	11	
Average	18	5	42	15	24	23	

* Records inadequate.

an average onset on the fifteenth day. The change was noted to persist for various periods of time ranging from 1 to 72 days; the average duration was 24 days (Table 1 and Case Histories).

Shookhoff and Taran[6] noted similar *T*-wave changes as early as the fourth day of illness and as late as the fifty-seventh day with a return to normal in a period of 7 to 63 days. The data presented here are essentially in agreement with their observations.

Alstead[1] believes that the *T*-wave change is not indicative of serious myocardial damage and that the myocardium returns to normal with the return of the normal *T* wave. Nathanson,[5] however, studied 15 ambulatory cases of convalescent diphtheria and found 7 with abnormal *T* waves. Two of these patients died suddenly.

In our series death occurred in 3 of the 23 cases of *T*-wave change. One death was due to respiratory complications, 1 was probably due to a previous coronary disease and the third developed conduction changes.

Fatal terminations in this group of cases are not in agreement with our findings and we do not regard the *T*-wave changes to be of serious prognostic significance. Our experience may possibly be explained by the fact that we prescribed a period of complete inactivity for all the patients showing these alterations, until such time as the electrocardiogram had returned to normal.

Similar *T*-wave changes are noted in many febrile diseases such as scarlet fever, pneumonia, acute sinusitis, rheumatic fever and tonsillitis. They are frequently present in coronary disease and in patients who are adequately digitalized. With the exception of coronary disease the alterations are generally transitory and apparently the result of intoxication rather than structural damage to the myocardium. They appear to have little or no prognostic value. Our present studies of their occurrence in diphtheria would seem to show them to be similarly transient and largely without evil significance as to the patient's recovery.

Conduction Changes. The second group of electrocardiographic changes consisted of ventricular escape, prolonged *QRS* phase, intraventricular block and auriculoventricular (*A–V*) dissociation. Marked distortion of the *R–T* line, with depression or elevation in one or more leads, was of frequent occurrence. The cases showing intraventricular block presented electrocardiograms which closely approached those of a bundle branch block, but where there was doubt the records were interpreted as intraventricular block without further specific definition. Many cases showing *A–V* dissociation presented a terminal picture of ventricular tachycardia.

These conduction changes occurred in the more toxic cases, in the younger age group and, in sharp contrast to the changes in the *T* wave, proved to be of grave prognostic significance.

Of our series. 17 patients showed various types of conduction

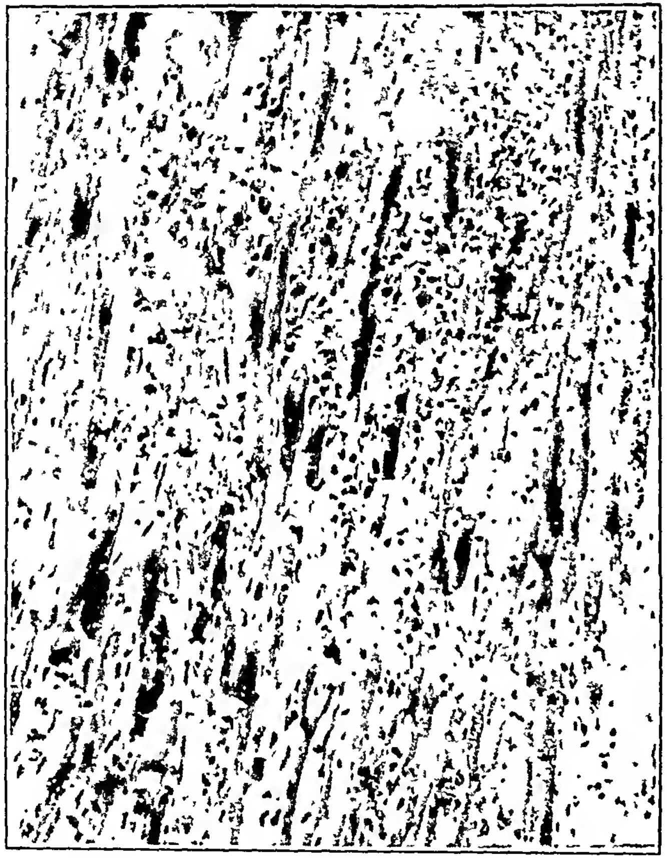

Fig. 1

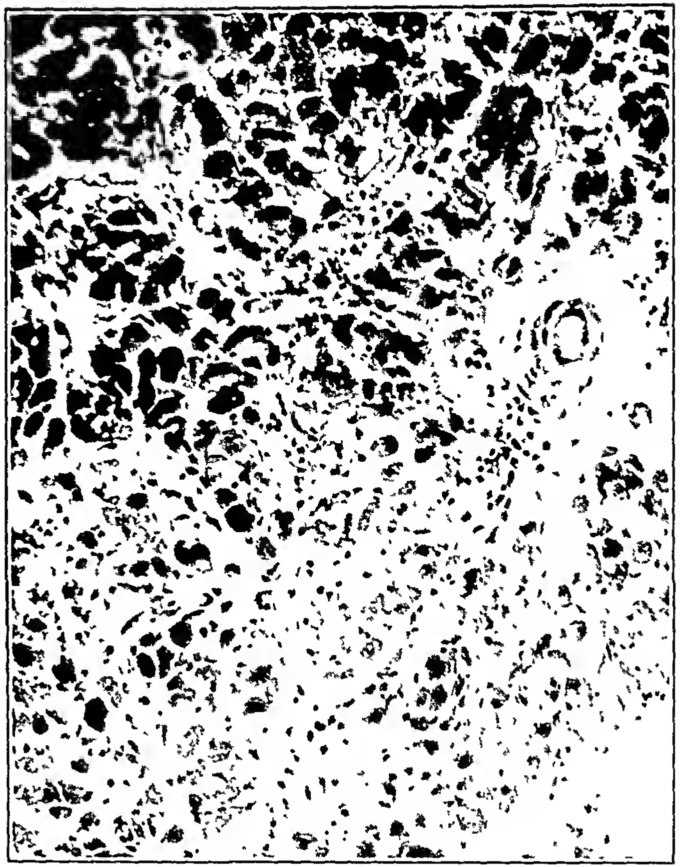

Fig. 2

Fig. 1.—Case 18. Female, aged 9. Death on ninth day of illness. Section from posterior papillary muscle. Note perivascular, patchy areas of intense leukocytic infiltration, associated with degenerative changes of muscle cells, generalized interstitial edema and congestion. See Fig. 6 for electrocardiogram.

Fig. 2.—Case 131. Female, aged 5. Death on tenth day of illness. Note acute myocardial degeneration with necrosis, leukocytic infiltration, hydropic and fatty changes.

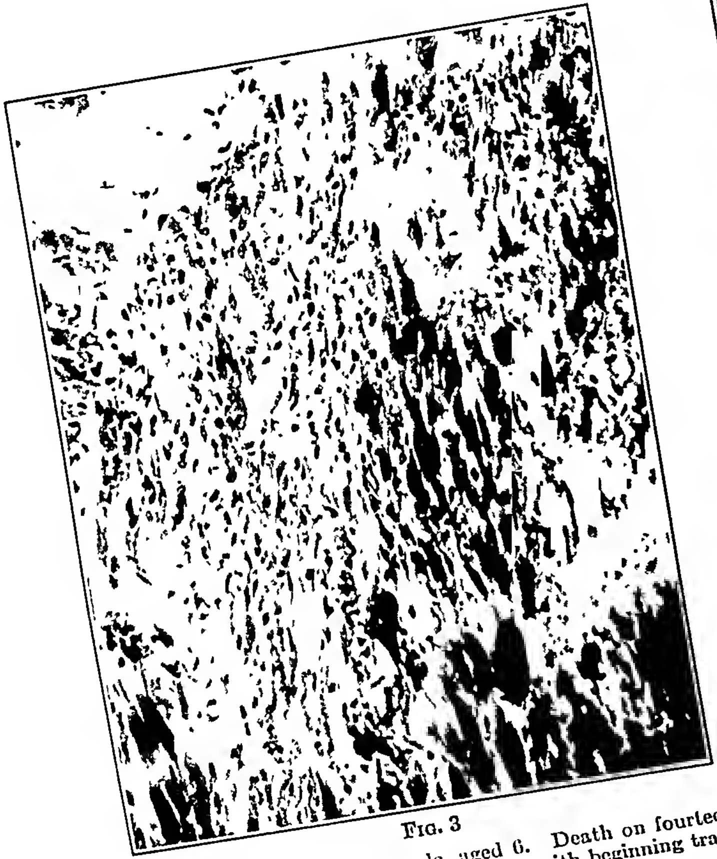

Fig. 3

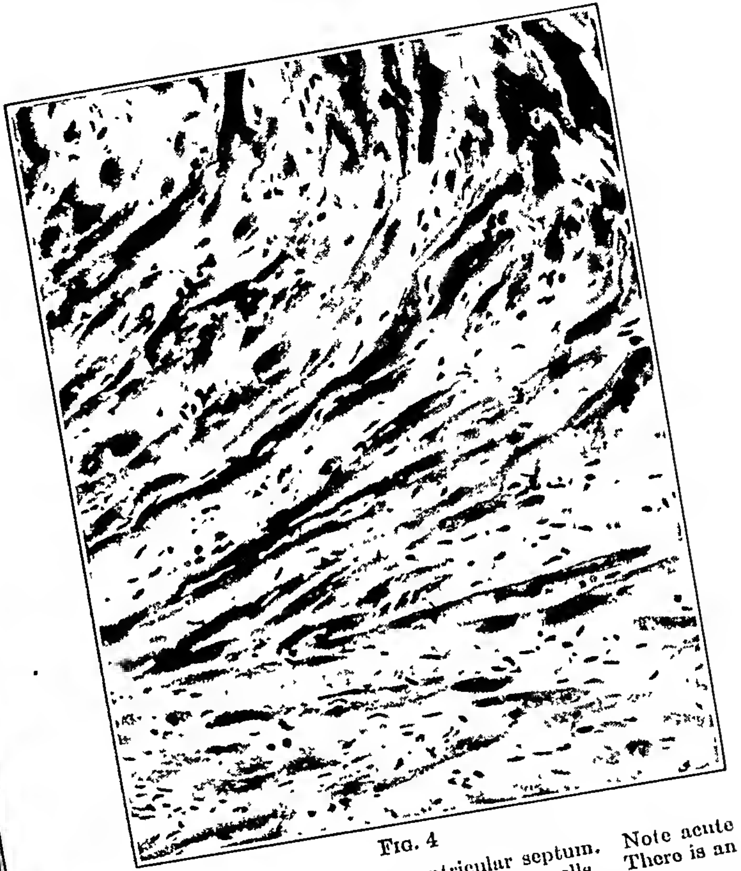

Fig. 4

Fig. 3.—Case 133. Female, aged 6. Death on fourteenth day of illness. Section from interventricular septum. Note acute degeneration and necrosis of the muscle with beginning transition of the exudate from polynuclear to monocytic cells. There is an early fibrosis.

Fig. 4.—Case 17. Female, aged 19. Death on sixty-first day of illness. Section from posterior papillary muscle showing late interstitial fibrous myocarditis.

FIG. 5

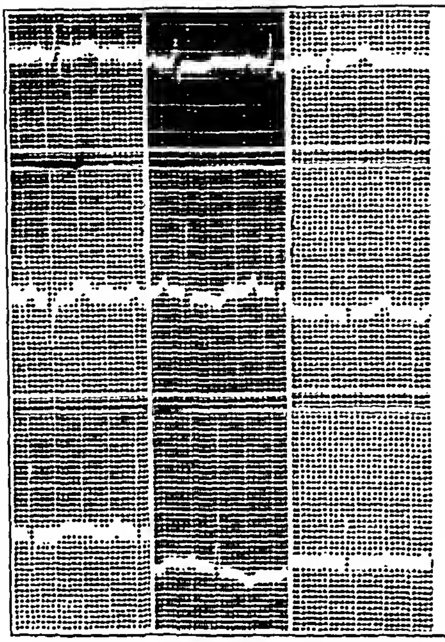

FIG 6

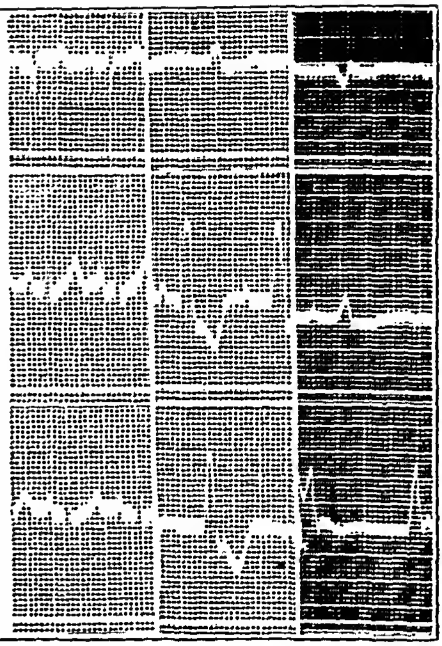

FIG. 5.—Case 5. Aged 28. Electrocardiograms on dates indicated. Note normal record followed by inversion of the *T* waves and subsequent return to normal. Patient recovered.

FIG. 6.—Case 18. Aged 9. Electrocardiograms on dates indicated. Note auriculoventricular dissociation in the second record. The excursions show a decreased amplitude in the final record. See Fig. 1. Patient died.

FIG. 7

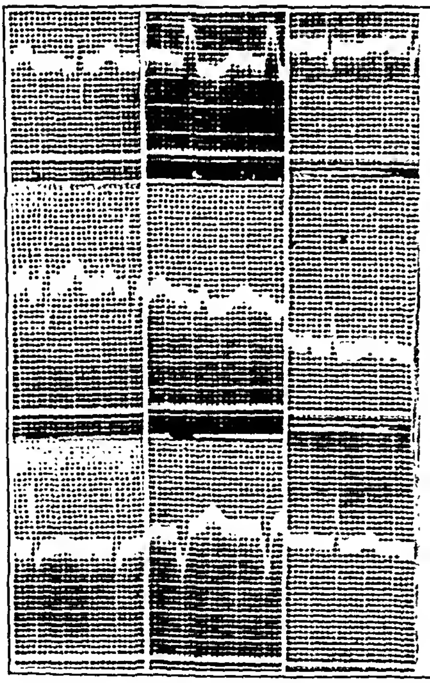

FIG. 8

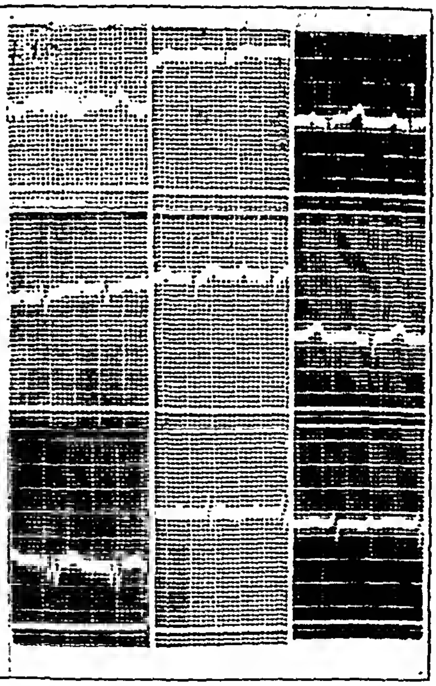

FIG. 7.—Case 41. Aged 5. Electrocardiograms on dates indicated. Note intraventricular block. The final record shows improvement. Patient recovered.

FIG. 8.—Case 10. Aged 3. Electrocardiograms on dates indicated. Note intraventricular block in the first record. The second record shows improvement but a first-degree block is present. The final record is normal. Patient recovered.

defects. The earliest occurred on the fifth day and the latest on the thirteenth day of illness. The changes occurred on the eighth day, as an average for the group. The conduction defect was noted to persist for various periods of time, ranging from 1 to 13 days; average duration, 5 days.

Eleven of the 17 patients developed *A–V* dissociation. This complication was invariably fatal, which accounts for the short duration of life recorded for this group.

Four of the 17 patients recovered. One of them demonstrated ventricular escape, a mild form of conduction block. One showed splintering and a prolongation of the *QRS* phase. Two presented intraventricular block without *A–V* dissociation. Two of the patients who recovered subsequently also developed *T*-wave changes on the tenth and fifteenth day, respectively, after the onset of the conduction change (Table 2 and Case Histories).

TABLE 2.—TOXIC DIPHTHERIA CASES SHOWING ELECTROCARDIOGRAPHIC CHANGES IN THE CONDUCTION SYSTEM.

Case No.	Age.	Days from onset of illness to antitoxin.	Amount of antitoxin in 1000 units.	Days from onset to conduction change.	Days duration of change.	Days from onset to peripheral nerve paralysis.	Comment.
2	6	2	34	7	5	12	*A–V* dissociation; died.
4	2	4	35	9	12	15	*A–V* dissociation; autopsy.
10	3	2	30	10	7	...	Intraventricular block.*
16	4	6	38	9	4	27	Ventricular escape.*
17	19	3	82	†	†	32	Autopsy; 61-day illness.
18	9	2	40	6	3	...	*A–V* dissociation; autopsy.
33	4	5	30	6	10	15	*A–V* dissociation; died.
40	8	3	25	7	1	...	*A–V* dissociation; died.
41	5	4	30	8	13	32	Intraventricular block.*
52	6	4	30	8	9	10	*A–V* dissociation; autopsy.
81	2	4	20	5	1	...	*A–V* dissociation; died.
89	2	5	25	10	2	...	*A–V* dissociation; died.
107	2	3	35	10	5	20	Splintering *QRS*.*
131	5	5	30	7	3	...	*A–V* dissociation; autopsy.
132	3	6	38	9	1	...	*A–V* dissociation; autopsy.
133	6	10	30	13	2	10	Intraventricular block; autopsy.
134	12	5	35	11	5	11	*A–V* dissociation; died.
Average	5	4	34	8	5	18	

* Indicates recovery. † Records inadequate.

Age. The *T*-wave changes occurred in all age groups. They were more prevalent, however, in the electrocardiograms from patients between 18 and 57 years of age.

The conduction changes occurred in the younger age groups. They were more frequent in the electrocardiograms from patients between 2 and 6 years of age. The oldest patient showing this type of change was 19 years of age.

Antitoxin. Antitoxin was given to every patient included in this series, with the exception of 2. These entered late in the disease after the acute symptoms had subsided.

Contrary to what might have been anticipated some of the most marked electrocardiographic and pathologic changes occurred in patients who had received large doses of antitoxin as early as the second and third day of illness (Table 2, Cases 2, 10, 18; Figs. 1 and 6.)

The 17 patients showing conduction changes received an average of 34,000 units of antitoxin on the fourth day (average) of illness. The *T*-wave alteration group of 23 patients received an average of 42,000 units of antitoxin on the fifth day (average) of illness. The value of antitoxin cannot be deduced from the data presented as all of the toxic patients received this specific therapy. It is shown, however, that even the early administration of antitoxin does not always protect the patient suffering from a virulent infection.

Nerve Palsies. The incidence of peripheral nerve palsies in the group of patients showing electrocardiographic changes was so frequent that we include data on their occurrence. The nerve damage was manifested by nasal voice, nasal regurgitation, extraocular motor paralysis and severe weakness of the extremities.

The palsies occurred late in the illness and were, therefore, prevalent in the group surviving the acute diphtheria and they bore no definite causal relation to the cardiac phenomena other, perhaps, than their prevalence in the more toxic cases. Peripheral nerve palsies occurred in 17 of the 23 patients showing *T*-wave changes, an incidence of 74%. The earliest occurred on the eighth day of illness and the latest on the forty-fifth; average onset was on the twenty-third day.

Paralysis occurred in 10 of the 17 cases showing conduction changes, an incidence of 59%. Early mortalities account for this low figure. The earliest paralysis in this group occurred on the tenth day of illness and the latest on the thirty-second day. The average occurrence was on the eighteenth day as contrasted to the 23-day average for the group showing *T*-wave changes.

The high incidence of peripheral nerve palsies in these groups of patients is of important clinical significance. We find that many cases showing clinical nerve palsies have an accompanying toxic myocarditis. When conditions do not favor the routine use of electrocardiograms the development of a nerve palsy should suggest the immediate need for special care and every effort should be made to secure one or more electrocardiograms. Absolute bed rest and a prolonged convalescence should be demanded.

Clinical Manifestations of Toxic Myocarditis. Dyspnea, edema and enlarged, tender liver, so often encountered in myocardial failure, were rarely found in this group of young patients. The symptoms generally encountered were similar in many respects to those of coronary disease. Precordial pain, arrhythmias and shock were the predominant symptoms. Such circulatory failure as was observed was of the peripheral vasomotor type, similar to that seen in other severe infectious diseases, or, at times, after surgical operations. The day to day cardiac auscultations proved to be a poor index to the appraisal of the myocardial function. *A–V* dissociation was often undetected until the electrocardiogram was obtained. Regular idioventricular rhythms of 80 to 90 per minute were not uncommon in the terminal phase of the diphtheria.

Marked arrhythmias, observed clinically, during the first 2 weeks of illness, caused us to suspect some major type of conduction block. This suspicion was generally confirmed by the electrocardiogram.

Marked *T*-wave alterations (diphasic and inverted) were always found during the convalescent stage of the disease. Routine clinical heart examinations revealed no signs of physical change with the possible exception of a tachycardia which was out of proportion to the temperature and clinical state of the patient. These facts lend support to the assumption that these changes are toxic rather than structural in nature.

The Pathologic Anatomy of Diphtheritic Myocarditis. It is our purpose to demonstrate the changes which occur in the myocardium and its conduction tracts in the fatal cases of diphtheritic myocarditis. We also attempt to correlate the anatomic changes with the alterations in the electrocardiographic tracings.

During the past 5 years we have had the opportunity of making complete anatomic studies in 100 cases of diphtheria. This represents approximately 54% of the total number of fatal cases, which in turn represents a mortality rate of 5.5% of 3220 diphtheria admissions at the Willard Parker Hospital during the same 5-year period. The correlated electrocardiographic and autopsy studies cover only a few selected cases on which serial electrocardiograms were obtained.

Broadly speaking, there is a rough parallelism between the degree of change in the conductivity as measured by the electrocardiograph, and the severity of the histologic changes in the myocardium. There is, however, a distinct lack of correlation between the electrocardiographic changes and demonstrable lesions in the conduction tracts.

We cannot outline the pathologic changes occurring in the myocardium in the *T*-wave alteration group. Death did not occur from this complication alone.

In the second group (7 cases) showing conduction changes electrocardiographically, there was a striking similarity in the tissue changes of the myocardium. In every instance there was more marked involvement of the contractile tissue than of the conduction tract.

Gross Lesions. It is a source of considerable surprise to the clinician when he attends an autopsy on one of his diphtheria cases, which has apparently died of myocardial failure, to have the pathologist find little or nothing to demonstrate in the heart grossly.

Yet that is the picture which is usually present. Certainly, in the majority of cases the changes are so minimal that, even to one familiar with the appearance of the heart in acute infectious disease, there is very little to suggest any actual impairment of heart function or structure. In the average case the myocardium, at most, seems to have lost a little of its tone; in the more striking cases, to be actually flabby in consistency. There may or may not be an associated right-sided dilatation., The endocardium rarely shows any gross abnormalities, being smooth and glistening. The valves, in conjunction with the dilatation, may be slightly stretched at times, but there is ordinarily no apparent valvulitis. Section of the musculature may on occasion suggest very minor fatty degeneration with some intimation of "tigroid" mottling.

In the 7 severe cases with which we are particularly concerned in this discussion the picture is more definite. There is a frank myocardial degeneration with softening of the musculature, in at least 2 instances, to a degree where the examining finger perforates the wall because of its extreme friability. Its color is quite definitely yellowish due to extensive fatty degeneration. In most of these cases, agonal or antemortem thrombi are found in the auricular appendage of the right side. In 1 instance (Case 52) a similar thrombosis on the interventricular septum was noted in the left ventricle. No grossly demonstrable changes involving the valves could be found.

The microscopic picture is likewise apt to be disappointing in the majority of cases in comparison with the clinical evidence of myocardial failure of which the patients seem to die. In this limited group of cases in which correlated studies of the electrocardiograms and the tissue changes were conducted, they appeared much more startling and severe. In our series we have progressive lesions ranging from practically *nil* to the most profound. These occurred in cases dying from the third day of the disease up to the sixty-first. No parallelism is noted in the time relationship in general, as we have cases dying in less than a week with very marked changes, and cases dying in the third and fourth week showing little or nothing histologically. On the other hand, in studying the pathologic changes of the entire 100 cases we find that the peak of the acute picture occurs somewhere between the tenth and the nineteenth day of illness. In those patients dying later than this the reparative features predominate.

In spite of the marked alteration in conductivity as shown by the electrocardiograms, the lesions of the conduction system are usually much less marked than the general myocardial damage. This has been demonstrated by silver stains of the nerve structure and by a few sections stained for glycogen by Best's carmine method.

The histologic features of diphtheritic myocarditis may be summed up very simply. First, there is a progressive interstitial edema and congestion of the myocardium which may or may not be demonstrable in the conduction bundles, but which is usually especially notable in the auricular musculature, the papillary muscles of the right and left ventricles and the interventricular septum, in that order of frequency.

In the second place, we have a perivascular leukocytic infiltration of the stroma of increasing degree. This extends in the more severe cases throughout the musculature, but is apt to be patchy and irregular in its distribution. At times it becomes the predominant feature of the picture (Fig. 1). Associated with this interstitial myocarditis, we find varying degrees of degeneration of the muscle fibers: fatty and hydropic changes, swelling, loss of staining capacity, ultimately loss of striation, nuclear degeneration, usually of a karyolytic nature, and finally actual necrosis (Fig. 2). This parallels closely, of course, the gross changes already described. Whether these degenerative changes are the result of direct action of the toxin on the muscle fibers or follow indirectly as a result of the exudate, is difficult to ascertain, but arguing by analogy we believe the former to be true.

At this stage of the acute inflammatory process the reparative factors of transition of the exudate from the neutrophil to the mononuclear type and the new growth of fibroblasts sets in (Fig. 3). This is best demonstrated by special connective-tissue stains. For the most part, these severe myocardial changes have very closely paralleled the changes seen in the electrocardiographic record.

In the late picture, which we had the opportunity of seeing in 1 patient who died on the sixty-first day of illness, we find a typical diffuse fibrosis of the myocardium, comparable to the chronic interstitial fibrous myocarditis which we commonly associate with nutritional interference and resultant sclerotic changes in middle or later life (Fig. 4). We do not wish to overemphasize this picture, but we believe that individuals who have suffered from toxic diphtheria in childhood, especially with suggestive heart involvement, may represent potential cardiac invalids. The factor of safety in these hearts must be impaired by the scarring and functional hypertrophy of the remaining musculature.

Councilman, Mallory and Pearce[2] state that it is possible that diphtheria may lead to extensive formation of connective tissue and some of the cases of fibrous myocarditis may be due to it.

Only by following a series of such cases to middle life can an accurate determination of this relationship, if any, be made.

Case Histories. The following case histories illustrate the clinical course of patients demonstrating electrocardiographic changes, as described in the text. The pathologic findings are described in 2 of the 5 cases.

Case 1.—*Changes in the T wave.* D. C. (No. 2169; 1932) (series Case 5), a male cab driver, aged 28, developed a sore throat on April 12. Local physician incised infected area. He became progressively worse the next 2 days and was then given 10,000 units of diphtheria antitoxin intravenously on the fifth day of illness. Admitted to the hospital on April 17 where 20,000 units of antitoxin were given intramuscularly and a similar amount given intravenously.

Physical Examination (*Positive Findings*). Dysphagia and irritating cough were present. There was a thick gray membrane over the tonsils, uvula and soft palate. The neck showed bilateral confluent cervical adenitis. A throat culture showed Klebs-Loeffler bacilli.

Progress notes: April 18, Ekg. Rate, 108; *P–R*, 0.16 sec.; *QRS*, 0.06 sec. Sinus tachycardia. April 20, patient appeared toxic. Heart sounds normal, throat very sore. No edema or petechiæ. April 21 (see Ekg., Fig. 5). Rate, 74; *P–R*, 0.16 sec.; *QRS*, 0.07 sec.; normal record. April 23, gray membrane still covered throat. Ekg. as on April 21. April 24, throat improved, voice good. Heart, first sound at apex prolonged. Liver and spleen not enlarged. No edema. April 27, general condition much improved. No murmurs. No evidence of cardiac insufficiency. Ekg. showed initial inversion of T_2 and T_3. Rate, 65; *P–R*, 0.18 sec.; *QRS*, 0.06 sec. May 7, inversion of *T* wave in all leads. These changes continued until June 1. May 10, nasal voice first noted, regurgitation of food. Cough present. June 13, developed severe hyperesthesia of the extremities with a moderate degree of paralysis of the muscles of the feet, legs, hands and arms, Fig. 5, June 16, normal record. This had not entirely cleared on August 14, the day of discharge. June 16 (following year) Ekg. normal.

CASE 2.—*Auriculoventricular dissociation.* E. M. (No. 1959; 1932) (series Case 18), female, aged 9, developed a sore throat and fever on April 5, admitted to hospital April 7 acutely ill, when 20,000 units of diphtheria antitoxin were given intramuscularly and an equal amount given intravenously.

Physical Examination (*Positive Findings*). Toxic in appearance. Thick nasal discharge. Extensive dirty membrane covering the tonsils and soft palate. Marked cervical adenopathy typical of a "bullneck." Nose and throat cultures showed Klebs-Loeffler bacilli.

Progress notes: April 8, Ekg. Rate, 103; *P–R*, 0.14 sec.; *QRS*, 0.05 sec.; right axis deviation (Fig. 6); temperature, 101° F. Very toxic—general condition poor. April 9, heart sounds of poor muscular quality. Trace of albumin in urine. April 10, condition much worse, poor renal output. Pitting edema over tibiæ. April 11, Ekg. Auriculoventricular dissociation. Auricular rate, 105; ventricular, 86. Pulse regular, between 80 and 90. April 12, glucose infusion given. Marked pallor present. Ekg. as April 11, except ventricular rate, 56. April 13, very toxic. Heart sounds not remarkable. Ekg. except auricular rate, 122; ventricular rate, 75. The excursions showed a decreased electrical potential as compared with previous records. Patient suddenly vomited, developed generalized spasm, heart sounds became distant with rate of about 200 to 220 per minute. This continued for 10 to 15 minutes and the patient died. A terminal Ekg. was not obtained.

Summary of Case 2 (autopsy findings). The heart is enlarged. There are no valvular defects, but there is a definite, grossly demonstrable myocarditis, with several subintimal petechiæ. There is fatty mottling and loss of muscle tone of the myocardium. Microscopically, there is a very marked, acute myocarditis, characterized by interstitial edema, congestion, considerable mononuclear cellular infiltration, and beginning fibrosis. The muscle fibers show fragmentation, fatty hydropic degeneration, and in many places hyalinization is present (Fig. 1). The lesions of the heart seem to be fairly uniform and involve the entire musculature. There is no particular predilection for the conduction system and the bundle of His shows rather less extensive changes than does the rest of the musculature. The lungs show a terminal hemorrhagic bronchopneumonia, limited to the right side. The abdominal viscera present no pathologic changes beyond moderate toxic, degenerative changes.

CASE 3.—*Intraventricular block.* E. B. (No. 4125; 1933) (series Case 41), female, aged 5, developed a nasal discharge, cervical adenitis and vomited on June 5. Admitted to hospital on June 8 where 15,000 units of diphtheria antitoxin were given intramuscularly and an equal amount given intravenously.

Physical Examination (Positive Findings). Very toxic. Marked bilateral adenopathy ("bullneck"). Tonsils, uvula and soft palate were covered with a gray membrane. Nose and throat cultures showed Klebs-Loeffler bacillus.

Progress notes: June 9, Ekg. Rate, 96; *P–R*, 0.16 sec.; *QRS*, 0.06 sec. Right axis deviation. No murmurs. June 10, Ekg. as June 9 (Fig. 7). June 12, short systolic apical murmur developed. Ekg. Rate, 98; *P–R*, 0.16 sec.; *QRS*, 0.11 sec. Depressed *S–T*. Diagnosis: intraventricular block. This block continued with a decreasing *QRS* interval until June 22. Ekg. showed splintering of *QRS* in all three leads. June 24, Ekg. returned to normal. Rate, 95; *P–R*, 0.18 sec.; *QRS*, 0.05 sec. Heart sounds of good quality. General condition much improved. July 7, developed nasal voice; July 27, voice clear. Aug. 1, discharged cured.

CASE 4.—*Intraventricular and first-degree block.* H. F. (No. 733; 1932) (series Case 10), male, aged 3. February 10, developed sore throat and vomited. Admitted to hospital February 12, where 20,000 units of diphtheria antitoxin were administered intravenously (10,000 units next day).

Physical Examination (Positive Findings). Acutely ill. Serosanguinous nasal discharge, gray membrane on both tonsils and soft palate. Cervical nodes enlarged. Nose and throat cultures showed Klebs-Loeffler bacilli.

Progress notes: February 23, Ekg. Rate, 120; *P–R*, 0.16 sec.; *QRS*, 0.12 sec. Slurred *QRS* in Lead 1 (Fig. 8). Splintered *QRS* in Leads 2 and 3. Intraventricular block. February 27, signs of cardiac decompensation. Liver border to umbilicus, slight pre-tibial edema. Frequent premature ventricular contractions. Digitalized. March 1, Ekg. Rate, 112; *P–R*, 0.16 sec.; *QRS*, 0.06 sec. Low potential throughout. Slight splintering *QRS* in all leads. March 2, vomited. Heart sounds of poor quality. No liver tenderness or enlargement. No murmurs. March 5, Ekg. Rate, 94; *P–R*, 0.2 sec., *QRS*, 0.06 sec. Low potential throughout. March 10 to 14, vomited daily. March 14, otitis media. March 19, Ekg. Rate, 92; *P–R*, 0.23 sec.; *QRS*, 0.06 sec. First-degree block. March 20, slight pretibial edema. March 24, Ekg. Rate, 94; *P–R*, 0.18 to 0.2 sec.; *QRS*, 0.06 sec. A tendency to migratory pacemaker. March 26, systolic apical murmur developed during the last 3 days. Rhythm regular. Heart not enlarged. March 28, Ekg. Rate, 103; *P–R*, 0.14 sec.; *QRS*, 0.04 sec. Normal record. April 2, murmur still present. April 5, patient developed scarlet fever. April 25, developed measles. During the course of these two cross-infections the contour of the electrocardiogram did not change. May 5, patient discharged cured, Ekg. normal.

CASE 5.—*Fibrosis of myocardium.* A. M. (No. 258; 1932) (series Case 17), female, aged 19, developed a sore throat and vomited on January 15. Admitted to hospital January 18 with severe sore throat and swelling of neck. Diphtheria antitoxin (22,000 units) were administered intravenously just before admission. On admission, 15,000 units were given intravenously and a similar amount given intramuscularly. January 19, 15,000 units intravenously.

Physical Examination (Positive Findings). Heavy adherent gray membrane of soft palate extending to midportion of hard palate covering the fauces and obstructing the larynx. Cervical adenitis ("bullneck"). Nose and throat cultures showed Klebs-Loeffler bacilli.

Progress notes: January 20, worse. Breathing difficult from throat edema. Edema of scalp and "bullneck." Petechiæ over body. Diphtheria antitoxin (15,000 units) given intravenously. January 21, prognosis probably fatal in 48 hours. B.P., 110/84. January 23, some improvement. No heart murmurs. January 24, 20 cc. 50% glucose given intravenously and 10 units of insulin. January 25, no edema. No signs of heart failure. January 27, severe precordial pain; vomited. February 1, no edema, improved. February 12, condition very good. February 17, nasal voice (34th day illness). February 24, vomited, difficult swallowing. March 1, first Ekg. taken (first case studied and few tracings obtained). Rate, 84; *P-R*, 0.15 sec.; *QRS*, 0.06 sec.; slurred *QRS* in Leads 2 and 3. Diphasic T_2, negative T_3. March 6, Ekg. as on March 1. Vomited. March 11, occasional premature ventricular contraction. March 12, Ekg. as on March 1. March 14, heart sounds of good quality. No murmurs. March 20, vomited, and temperature progressed to 102° F. No edema. Patient suddenly became restless with severe coughing. Appeared very toxic. Examination showed heart to the right with apex beat at left sternal border. Resonance over entire right lung field with marked diminution of breath sounds. Diagnosis: massive collapse of right lung. Sudden death (61st day of illness).

Summary of Case 5 (autopsy findings). Terminal diffuse bilateral bronchopneumonia superimposed on a collapse of the right lung.

The heart is moderately dilated; myocardium, pale and flabby. There are no valvular or endocardial lesions. Sections microscopically through the heart show a diffuse generalized myocarditis in the stage of repair. The most striking finding is a very extensive fibrosis. This is relatively early, as evidenced by the large number of nuclei and the comparatively small amount of collagen. There is still considerable cellular infiltration, chiefly about the blood-vessels, but extending into the interstitial tissue. The cells are mostly of the monocytic series, including lymphocytes, plasma cells and large mononuclear phagocytes. No greater involvement of the bundle of His is noted than of the musculature in general (Fig. 4). The remainder of the visceral lesions are of relatively slight significance. There is an associated toxic hepatitis, splenitis and toxic degeneration of the renal tubular epithelium.

Summary and Conclusions. 1. Serial electrocardiograms were made on 140 patients showing evidence of toxic diphtheria; 28 of these showed changes in the contour of the electrocardiograms.

2. The electrocardiographic changes were divisible into two groups comprising *a*, alterations in the *T* wave, and *b*, alterations in the conduction system.

3. Twenty-three patients showed the *T*-wave changes occurring between the fifth and thirty-ninth day of illness. A majority of the changes occurred between the eighth and fifteenth day of illness.

4. Seventeen patients showed conduction changes between the fifth and thirteenth day of illness; 11 of these patients developed *A–V* dissociation. This complication invariably proved fatal.

5. Fourteen patients, showing electrocardiographic changes, died of toxic diphtheria; 7 of these received large doses of diphtheria antitoxin on or before the fourth day of illness. Early administration of antitoxin did not save this group of patients.

6. Peripheral nerve palsies occurred in 65% of the patients

presenting electrocardiographic changes. The paralysis apparently bore no causal relationship to the cardiac phenomena.

7. There was a rough parallelism between the conductivity as shown by the electrocardiogram and the microscopic changes in the myocardium as demonstrated in the 7 cases of this series that were autopsied.

8. The essential histologic changes in the myocardium due to toxic diphtheria are shown to be progressively, edema, congestion, cellular infiltration, degenerative changes in the muscle fibers and ultimate fibrosis.

9. These lesions, found at autopsy, suggest that diphtheria may be one of the causes of chronic fibrous myocarditis in patients who survive the more toxic state.

10. The electrocardiographic findings constitute an important guide in the treatment of. diphtheria. Complete inactivity is recommended for those showing abnormal electrocardiograms until the electrocardiogram has had ample opportunity to return to normal.

The technical work (electrocardiographic) for this paper was preformed by Miss Marion Frank, R. N.

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THE EFFECTS OF CAROTENEMIA ON THE FUNCTION OF THE THYROID AND THE LIVER.*†

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Avitaminosis has received much attention in medical literature in the past few years, but few reports have appeared on hypervitaminosis. It has been maintained§ that carotene is non-toxic

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* Supported, in part, by the Christine Breon Fund for Medical Research.

† With the technical assistance of Mrs. Media Orem Dahl, A.B., Mrs. T. B. Leake, A. B., and Miss Mabel Stockholm, A.B.

‡ Now with the Council of Medical Education and Hospitals of the American Medical Association.

§ The Non-toxicity of Carotene. Abstracts prepared by the Research Department of S. M. A. Corporation, Cleveland, Ohio.

and may be used therapeutically in large amounts. While it is not likely that the excessive use of therapeutic preparations of carotene will produce carotenemia, we have seen carotenemia in patients who have been on abnormal diets which contained large amounts of vitamin A and its precursors. We are reporting in this study certain untoward effects which have followed the use of such diets and which should be recognized, especially disturbances of the thyroid and the liver.

There is considerable laboratory and clinical evidence suggesting a possible antagonism between carotene and thyroxin. In 1932, Euler[4a] fed rats a diet deficient in vitamin A but which contained adequate amounts of vitamins B, C and D. Carotene and thyroxin were then administered to one group, thyroxin alone to another and carotene alone to a third. The first group gained an average of 1 gm. per day in body weight; the second lost 9 gm. a day; while the animals receiving carotene without thyroxin gained 11 gm. daily. The administration of carotene with thyroxin seemed to compensate for the loss in body weight due to the administration of thyroxin alone. In another experiment on rats, Euler[4b] fed a diet deficient in vitamin A and found that a partial inactivation of thyroxin occurred, possibly due to fixation or binding of the thyroxin by the carotene.

Euler refers to the work of Abelin[1a] who confirmed his observations. He used guinea pigs kept on a diet deficient in vitamin A. Abelin also found that when colloidal carotene was mixed with thyroxin and allowed to stand in a stream of air in an incubator, in 4 or 5 instances the thyroxin content of the mixture decreased approximately 22.5%. The author implies that no change in thyroxin content occurred using thyroxin alone.

Parhon and Werner[9] gave 500 units of thyrotropic hormone to ducks over a period of 5 days and found the mean blood carotene content to be 0.453 mg. per 100 cc., whereas controls had 0.664 mg. per 100 cc. The ducks given the hormone alone lost 6.33 gm. per 100 gm. during the period of experimentation.

Wendt[11] reported low serum carotene and vitamin A in Basedow's disease, but following treatment with iodine or by thyroidectomy the vitamin A content of the serum was increased. When he gave large doses of vitamin A to 5 patients with hyperthyroidism who had previously responded poorly to other methods of treatment, 3 gained weight, had decreased metabolic rates, and showed subjective and objective improvement. Abelin[1b] also suggested that vitamin A be used as an adjunct to iodine in the treatment of hyperthyroidism. He believed, however, that a definite evaluation of this procedure was not possible.

Laubmann[6] found that when rats were given toxic amounts of vitamin A they showed slight parenchymal changes in the liver and the spleen, and died as a result of glomerulonephritis. It is difficult[3] to cause hypervitaminosis A in animals by feeding excessive amounts of carotene, since the liver of rats absorbs but a small amount of carotene as compared with absorption of vitamin A. Animals and men are known to store large quantities of vitamin A in the liver, so that as much as 95% of the total amount distributed in the body may be recovered from this organ. Ocana[7] noted an increased content of fat in the cells of the livers of rats given large doses of carotene. This investigator fed toxic amounts of extracts of carrots to rats and was able to produce lipoidosis of the cells of the liver. It is conceivable, therefore, that excessive carotene or vitamin A in the liver might cause some impairment of hepatic function.

Several workers have reported an increased cholesterol of the blood serum of rats and men in hypervitaminosis A.[5] Lasch[5] believed this was due to a direct action of the vitamin on the liver. Pasternak and Page[10] studied the action of thyroxin on lipoid metabolism and found that the iodine number was increased 50% in the muscles of thyroxin-injected rabbits, but there was no increase in the cholesterol content. The fat and fatty acids in the muscle were decreased. There was little change in these constituents in the liver, brain and blood except that the liver had an increased cholesterol in the rabbits treated with thyroxin. Parhon and Ornstein[8] reported that daily doses of 1 mg. of thyroxin given to patients for 2 to 3 days decreased their cholesterolemia as well as the fatty acids and total lipids in the blood.

These observations suggested to us the hypothesis that patients with carotenemia might exhibit clinical evidence of hypothyroidism or hepatic insufficiency.

We have reviewed 13 patients with carotenemia,* in 9 of whom functional tests of the thyroid and liver were made. All of the patients were adults, aged 19 to 65 years; 7 were males. Nine lived in rural districts of California, and of these 5 were farm residents. The diagnosis of carotenemia was made by observing the yellowish discoloration of the skin, which was noted in the palms of the hands and the soles of the feet. The scleræ were not discolored nor did other areas of the skin show perceptible changes in color. Since Baur[2] has shown that carotene in solution was changed chemically on exposure to light and air, it seems likely that this photo-oxidative effect is more pronounced on surfaces of the body other than the palms and soles. The clinical diagnosis was substantiated in all cases by the appearance of carotenoid coloring of petroleum ether when shaken with a specimen of the blood serum from which protein had been precipitated by alcohol. No quantitative estimate of carotene was attempted.

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* Five patients included by courtesy of Dr. Alfred C. Reed; 2 by courtesy of Dr. Wm. J. Kerr; and 1 by courtesy of Dr. I. C. Schumacher.

TABLE 1.—SIGNIFICANT FINDINGS IN 9 PATIENTS WITH CAROTENEMIA.

Initials and case No.*		Diagnoses other than carotenemia.	Approximate weight on entry in kg.	Duration of abnormal diet.	Estimated loss of weight in kg.	Basal metabolic rate, %.	Rose-Bengal test,† % dye remaining in blood after:		Plasma cholesterol, mg. %.	Total blood lipids,‡ gm. %.	Total phenolsulphonephthalein excreted in 2 hrs., %.	Other observations including complaints.
							8 min.	16 min.				
M. A.	1	Bursitis; hepatic insufficiency	60	1 yr.	3.6	−10.7	75	44	208	1.66	...	Lived on farm; dieted for "constipation."
V. H.	2	Fibroid tumor of uterus; hypothyroidism	62	1 mo.	3.2	−18.0	62	30	197	2.00	...	Urban resident; dieted for "constipation."
O. J.	4	Hypothyroidism; hepatic insufficiency	63	2 yrs.	6.1	−40.7§	62	44	238	...	...	Lived on farm; complained of epigastric pain, bloating.
J. H.	5	Hepatic insufficiency; chronic prostatitis	70	Not known	0	...	84	52	...	...	65	Farmer; suffered nocturia, complained of bloating.
K. N.	6	Hepatic insufficiency; anxiety neurosis	74	2 mos.	3.2	...	80	61	...	...	100	Farmer (tractor mechanic); had epigastric pain, bloating.
W. N.	7	Chronic cholecystitis; without hepatic involvement	65	6 mos.	18.0	...	42	36	...	...	...	Rural resident; complained of epigastric pain.
J. S.	8	Hypothyroidism; malnutrition	73	4 yrs.	20.9	−22.0	52	31	...	...	...	Farmer; suffered pain in epigastrium.
C. R.	12	Chronic cholecystitis; cholelithiasis; cirrhosis of liver; hypothyroidism	56	2 yrs.	5.6	−25.9	...	...	204	1.70	47	Rural resident; had epigastric pain, "constipation."
C. M.	13	Trigeminal neuralgia; arteriosclerosis; hypothyroidism	62	10 yrs.	6.0	−20.4	50	15¶	252	1.80	58	Rural resident; had upper lip pain and "neuritis."

* Cases 3, 9, 10 and 11 are not included because of incomplete laboratory data.

† Percentage remaining in blood normally is 55 ± % at 8 minutes and 35 ± % at 16 minutes.

‡ Method of W. R. Bloor (J. Biol. Chem., 23, 317, 1915). (Normal values, 0.67 to 0.72 gm. %.)

§ On discharge from hospital the blood serum showed no carotenoid discoloration and the basal metabolic rate was −19%.

¶ Courtesy of Dr. Jesse Carr.

... No test done.

The carotenemia was due in each case to the substitution of vegetables, fruit and milk rich in carotene for other foods. It was apparently self-induced in 10 cases; 3 patients developed carotenemia on diets prescribed for peptic ulcer, diabetes mellitus and asthma, respectively. None of these patients sought medical care because of carotenemia. Table 1 summarizes the significant findings in 9 patients.

The most consistent finding in this group is the loss of weight during the period of dieting. Five (Cases 2, 4, 8, 12, 13) of the 7 patients in which the thyroid status was studied had clinical and laboratory evidence of hypothyroidism. The sixth patient (Case 1) had impaired hepatic function, a metabolic rate of −10.7%, but was not thought to be hypothyroid. In the seventh patient (Case 10), the determination of the basal metabolic rate was reported to be unsatisfactory. Only 1 patient with hypothyroidism had hepatic insufficiency. The 2 remaining individuals with hepatic dysfunction had no obvious cause other than carotenemia for this condition. Hepatomegaly occurred in 4 patients (Cases 1, 2, 6, 12) and tenderness in the right upper abdominal quadrant in 2. Rose-Bengal tests for hepatic function were made on 8 patients (serum concencentration of the dye was determined colorimetrically in specimens of venous blood withdrawn 8 and 16 minutes after 100 mg. of the dye had been injected intravenously). The blood lipids were significantly elevated in the 4 cases examined.

Icteric indices were elevated, presumably because of the carotenoid coloring of the blood serum. Van·den·Bergh tests were normal in the 6 patients tested. Routine blood, urine and stool examinations were normal except in Case 4 who had secondary anemia, and in Case 5 who had prostatitis. Blood Wassermann tests in 12 patients were negative. There were no other significant objective or subjective findings relating to carotenemia in these patients.

We may say, then, on the basis of our findings in 5 patients with carotenemia, that there is evidence indicating that an antagonism exists between carotene and thyroxin. Of the 5 patients with evidence of hypothyroidism, 1 had hepatic insufficiency; 3 others had laboratory and clinical evidence of hepatic dysfunction. It seems possible that carotenemia may have contributed to the dysfunction of the thyroid and of the liver in these individuals. Unfortunately, we have no data as to the status of these patients before the appearance of carotenemia. It is possible that in Case 8, malnutrition may have contributed toward the lowered metabolic rate.

Conclusions. Carotenemia and its complications deserve more serious consideration as a symptom complex or as a disease entity. Eight of 9 patients with carotenemia on whom functional tests were made had disturbances of the thyroid or liver or both. These could be best explained on the basis of Euler's suggestion that carotene antagonizes thyroxin, and on the evidence presented that carotene damages the liver.

Note.—Dr. Wm. J. Kerr suggests that perhaps a primary injury of the liver may prevent the conversion of carotene and its storage as vitamin A. Thus from the evidence presented, hepatic insufficiency may be regarded as the cause rather than the effect of oversupply of vitamin A in the diet. Perhaps these patients had previous hyperactivity of the thyroid over long periods, and this resulted in hepatic injury. Following hyperplasia of the thyroid or "thyroiditis," hypothyroidism may occur. If vitamin A and thyroid function are antagonistic, a deficiency of the liver may prevent both the extraction of vitamin A and conversion of carotene which, being unchanged, is not available for storage as vitamin A and appears in the blood and tissues in the clinical state of carotenemia.

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BLOOD SUGAR DURING LABOR, AT DELIVERY AND POST-PARTUM, WITH OBSERVATIONS ON NEWBORNS.

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From time to time, various investigators have studied the blood-sugar values during pregnancy, at delivery and during the puerperium. Most of this work has been a matter of record for a number of years, during which period our knowledge of glucose metabolism has advanced rapidly and obstetrical practices have undergone great changes. Moreover, chemical techniques have been developed which enable us to follow with frequency and safety the blood-sugar values of newborns. In the light of this newer knowledge, it has seemed desirable to review the obstetrical blood-sugar values and contribute the blood-sugar values of newborns.

As the first step in our studies of glucose metabolism in obstetrics, we wish to report a series of blood-sugar values for normal mothers and infants at delivery. This work has been supplemented by blood-sugar determinations during the first stage of labor, during the puerperium, and on the infants of these mothers during the first 3 days of life. We have to a certain extent been guided by Morriss,[2] feeling that his work on this subject represents the most complete study of blood sugar in pregnant women at delivery, and that this approach provides a means of comparison which renders our work more valuable from an obstetrical and laboratory point of view.

In 1917, at the time of Morriss' study, the most widely used test for blood sugar was that of Lewis and Benedict, in which picric acid is converted to sodium picramate, and the resulting orange-red color read against a standard similarly treated. At the present time, colorimetric blood-sugar methods may be classified as macro, requiring amounts of blood necessitating venipuncture, and micro, requiring small amounts of capillary blood obtainable from skin punctures. It is extremely important to specify the method used for determination of blood sugar, and to give the corresponding normal range.

TABLE 1.—NORMAL VALUES OBTAINED BY COLORIMETRIC METHODS FOR BLOOD SUGAR.

Name of test.	Normal range, mg.	Type of test.
Folin-Wu, 1929	90–120	Macro; copper reduction.
Folin-Wu, modified	90–120	Micro; 0.1 cc. of blood.
Benedict, 1931	70–90	Macro; copper reduction.
Benedict, 1931, micro	70–90	Micro; 0.1 cc. of blood.
Lewis Benedict, 1913	90–120	Macro; picric to picramate.
Folin-Malmros, 1929	70–90	Micro; ferricyanide to ferrocyanide, 0.1 cc.
Jeghers-Myers modification of Folin-Malmros, 1930	70–90	Micro; 0.025 cc. of blood.

Former workers have used macro methods, necessitating the use of blood from venipuncture of the mother and from the cord of the infant, thus limiting the number of determinations. The work of Révész and Turolt,[4] who found that the blood sugar of the umbilical arteries was over 10% higher than that of the umbilical vein, indicates that cord blood is a mixture of uncertain composition so far as blood sugar is concerned. We feel that in using micro methods we are comparing the same type of blood from infant and mother, and enjoy an advantage in ease and safety of collection.

The method selected for determining the blood sugar in the present study was the Jeghers-Myers modification of the Folin-Malmros micro test, which is based upon the reduction of alkaline ferricyanide to ferrocyanide and subsequent color production with an acid ferric reagent. By running a series of standards equivalent to 70, 105, 140 and 175 mg. of glucose per 100 cc., accurate readings can be obtained over the range anticipated in this work. Precipitation of proteins directly from the capillary pipette used for collection prevents glycolysis. The use of this method makes it possible to run duplicates on the filtrate obtained from 50 cmm. of blood.

Unlike copper reduction tests ferricyanide reduction tests are not affected by auto-oxidation, and are therefore less susceptible to technical errors.

In our hands the modified Folin-Malmros test has given, in the great majority of determinations, an accuracy of within 3% on duplicates from the same filtrate. Several times the method has been checked by obtaining duplicate samples from the same skin puncture; such duplicates yielded results within 5%. To insure uniformity of technique, all blood samples were collected and all tests run by the same person. Workers familiar with colorimetric micro methods will realize that such tests are susceptible to an error of at least 3%,[3] and that the figures presented are possible only with great standardization of procedure. Table 2 summarizes the data on determinations made during the study.

Table 2.—Number and Percentage of Determinations on Mothers and Infants.

	Maternal.		Infant.		Total.	
Classification.	No.	%	No.	%	No.	%
No duplicate secured	31	11.4	81	29.6	112	20.6
Duplicates did not check	35	12.5	27	10.0	62	11.4
Duplicates check to 3%	205	76.1	165	60.4	370	68.0
Total determinations	271	..	273	..	544	

Of the 544 determinations run during the study, 432 (79.4%) were in duplicate; 62 (14.3%) tests run in duplicate did not check to 3%, usually for one of two reasons: (1) Low values difficult to compare due to light colors, (2) checks to 5% but not to 3%.

Following rigorous technique (cap and mask, preliminary scrub, sterile gown and gloves) samples of blood were collected from the heel of newborn infants as soon after delivery as respiration was well established, and at various intervals after birth. Because of this care, no complications were encountered during the study. Two infants developed chemical conjunctivitis which rapidly disappeared, and 1 infant showed signs of hemorrhagic disease of the newborn several hours after tests were taken. This infant later bled profusely from a slight self-inflicted scratch and from the umbilical stump, but recovered following a transfusion of whole blood.

Samples of the mother's blood were collected from the finger of the patient at the moment of delivery. No complications were observed in this group.

In view of the great difference in present-day obstetrical practices, we summarize here the care received by our cases during labor. Forty of the 50 cases were primiparæ, and received about the same type of care. The majority of them entered the hospital during the early stages of labor and were given morphine sulphate, $\frac{1}{6}$ grain, and scopolamine hydrobromide, $\frac{1}{150}$ grain, hypodermically, when contractions became uncomfortable. In 45 minutes this was followed by scopolamine, $\frac{1}{200}$ grain; and by a third dose of scopolamine,

$\frac{1}{400}$ grain, after another 45-minute period. Following this, patients received scopolamine, $\frac{1}{400}$ grain, at intervals of $1\frac{1}{2}$ hours until within 3 hours of expected delivery. Only occasionally was sodium amytal per rectum used, this drug being reserved for use in the multiparæ. With a few exceptions in which nitrous oxide was used, ether analgesia was given by the Gwathmey paper cone in the latter hours of the first and during the second stage of labor. All patients were anesthetized and the delivery, excluding breeches and versions, was effected by low forceps of the Tucker-McLane type, and was, in the great majority of cases, accompanied by mediolateral episiotomy. Pituitary extract (1 cc.) was given immediately after delivery, and ergotrate ($\frac{1}{320}$ grain) following the expression of the placenta. Mucus was removed from the baby's pharynx by catheter, and in some instances when respirations were shallow carbon dioxide, 5%, and oxygen, 95%, under pressure, were administered intermittently at normal respiratory rate.

In the multiparous group, the drug of choice was sodium amytal, 9 to 15 grains, per rectum, accompanied by ether analgesia in the latter part of labor, until delivery was possible. In this group Tucker-McLane forceps were also used in delivery of the head, but episiotomy was seldom necessary. The care of the baby was the same as in the primiparous group.

Our cases are unevenly distributed with regard to parity, since it is the policy at this hospital to deliver primiparæ in the hospital and most multiparæ in the home on the district service.

Table 3 lists the data on maternal blood sugar, infant blood sugar, total duration of labor, duration of the second stage of labor, duration of analgesia plus anesthesia prior to delivery, and notes on anesthetic, medication and type of delivery. Statistically, the proper treatment of this material to ascertain the interdependence of blood sugar and the various other factors has seemed to be the calculation of the Pearson rank-order coefficient of correlation.* These coefficients are incorporated in the table.

The mean blood sugars for mothers and infants are also shown in the table. The mean blood sugar for 10 multiparæ is 128.2, and for their infants, 101.7, all the determinations on infants being lower than those of their respective mothers. The mean maternal blood sugar for 40 primiparæ is 123.7, for their infants, 104.1. Three of the 37 infants had blood sugars slightly higher than those of their mothers, and the infant showing the greatest difference was 56.2 mg. less than his mother. The mean maternal blood sugar for the 50 mothers was 124.6, and for the 47 infants, 103.6. Fifty per cent

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* Coefficient of correlation is a statistical device for expressing, in a single figure, the relationship between two series of data. Perfect direct relationship is +1, while perfect inverse relationship is −1; in practice the coefficient is generally less than 1, since relationships are seldom perfect. The Pearson formula is $p = 1 - \frac{6\Sigma d^2}{n(n^2 - 1)}$.

TABLE 3.—DATA ON ROUTINE CASES.

Case No.	Blood sugar, mg./100 cc.		Labor, hours.		Anesthesia and analgesia.		Medication.	Notes.
	Mother.	Baby.	Total.	Second stage.	Type.	Hours.		
								Multiparæ.
51	96.8	86.6	11:10	:44	GOE*	:25	M&S, amyt.	Low forceps.
87	100.2	83.8	10:26	:56	GO†	4:55	Amyt.	Low forceps.
90	110.0	78.0	7:57	2:27	E‡	3:25	Amyt.	Mid-forceps, mod. Scanzoni.
56	116.8	78.2	20:10	1:10	E	1:30	Amyt.	Spontaneous.
36	121.8	115.4	9:57	:57	E	:40	M&S, amyt.	Low forceps.
65	128.0	116.1	24:37	:50	GOE	2:20	M&S	High forceps, mod. Scanzoni.
91	130.5	80.0	24:56	:56	E	5:20	Amyt.	Low forceps.
54	141.0	88.6	9:27	1:27	E	6:15	Amyt.	Low mid-forceps.
7	149.4	135.7	11:10	:44	E	6:30	Amyt.	Podalic version, breech extr.
29	187.4	154.4	22:15	3:15	E	1:40	M&S	Mid-forceps, axis traction, modified Scanzoni.
Mean	128.2	101.7	15:13	1:21				
								Primiparæ.
73	98.4	81.1	11:32	:32	E	1:30	Amyt.	Podalic version, breech extr.
45	102.5	84.0	..	..	E	:20	None	Spontaneous.
83	102.5	06.5	12:09	1:24	E	3:00	M&S	Low mid-forceps.
38	103.0	95.7	43:23	2:23	E	2:30	M&S	Low forceps.
46	104.5	74.1	12:08	2:08	E	3:15	M&S, amyt.	Podalic version, breech extr., epis.
4	104.7	..	33:50	1:50	E	1:45	M&S	Low forceps, episiotomy.
22	105.3	87.7	12:50	2:05	E	1:35	M&S	Low mid-forceps.
24	106.6	110.0	12:20	:35	E	2:25	M&S	Breech.
26	107.4	86.4	13:40	:35	E	3:10	M&S	Low mid-forceps.
63	107.5	117.6	8:27	:57	E	1:05	M&S, amyt.	Low forceps, episiotomy.
37	108.8	95.3	18:06	:51	E	2:45	M&S	Low mid-forceps, modified Scanzoni, episiotomy.
64	110.2	93.8	15:25	1:55	E	:35	Amyt.	Low mid-forceps, episiotomy
75	112.6	97.4	29:44	1:44	E	2:45	M&S, amyt.	Low mid-forceps, mod. Scanzoni.
58	114.8	97.4	13:32	1:07	E	2:05	M&S	Low forceps.
61	117.7	110.9	14:15	1:30	E	4:20	M&S	Low mid-forceps.
49	118.0	84.7	13:55	2:10	E	2:55	M&S	Low forceps.
43	118.0		7:50	1:50	E	2:40	M&S	Low mid-forceps.
71	120.7	119.3	15:26	1:06	E	1:15	M&S	Low forceps, episiotomy.
69	121.8	99.5	14:20	:50	E	1:10	M&S	Low mid-forceps, mod. Scanzoni.
13	122.5	..	10:36	:51	GO	1:05	M&S	Low forceps, 6 weeks premature.
12	123.3	99.0	8:55	:55	E	2:10	Amyt.	Low mid-forceps.
47	124.2	117.0	34:30	1:30	E	1:30	M&S, amyt.	Low forceps.
41	124.6	86.4	7:47	2:17	E	2:15	M&S	Low forceps.
70	124.8	102.7	7:07	:52	E	2:15	Amyt.	Low forceps, mod. Scanzoni.
28	124.8	114.7	14:47	5:02	E	2:25	M&S, amyt.	Podalic version, breech extr.
84	127.2	91.3	12:45	1:00	E	3:08	Amyt.	Low mid-forceps.
68	127.5	106.1	14:08	2:08	E	1:25	M&S	Low forceps, episiotomy.
40	129.2	108.2	12:55	2:10	E	2:10	M&S	Low forceps.
74	130.4	117.4	10:55	2:45	E	2:35	M&S, amyt.	Low forceps, episiotomy.
66	131.4	105.0	9:55	:55	GOE	:20	M&S	Analgesia only; spontaneous.
80	133.0	109.3	11:28	3:28	E	3:00	M&S	Mid-forceps.
21	135.5	140.0	12:05	1:35	E	2:20	M&S	Low forceps.
86	136.9	106.1	13:00	1:30	E	2:00	M&S	Low mid-forceps, mod. Scanzoni.
30	137.3	104.8	11:08	1:08	E	6:25	M&S, amyt.	Breech extraction.
34	137.7	122.2	11:23	2:23	E	3:30	M&S	Low forceps.
35	139.5	83.3	11:28	:28	E	2:15	M&S	Breech extraction.
77	147.8	105.8	41:31	2:31	E	2:05	M&S	Low mid-forceps, mod. Scanzoni.
39	148.3	121.9	16:16	2:16	E	1:55	M&S	Low forceps.
50	153.0	126.1	14:40	1:25	E	2:25	M&S, GOE	Low mid-forceps.
60	204.8	151.4	9:55	1:40	E	2:00	M&S	Low mid-forceps, episiotomy
Mean	123.7	104.1	15:20	1:39				

The mean of 50 maternal blood sugars is 124.6; for 47 infants, 103.6.

The Pearson rank-order coefficient of correlation between maternal and infant blood sugars for 10 multiparæ is +0.66; for 37 primiparæ, +0.59. The coefficient of correlation between duration of labor and maternal blood sugar for 10 multiparæ is +0.32; for 39 primiparæ, −0.17. The coefficient of correlation between duration of ether inhalation and maternal blood sugar for 41 cases which received only ether is +0.15.

* GOE anesthesia consists of a mixture of nitrous oxide, oxygen, and ether.

† GO anesthesia consists of a mixture of nitrous oxide and oxygen.

‡ E, ether.

of the multiparæ and 62.5% of the primiparæ fall between 110 and 140 mg. per 100 cc., figures approximately 50 mg. higher than the normal range for this method.

A further method of ascertaining the effect of anesthesia upon the rise in blood sugar is to exclude the factor of labor while holding the factor of anesthesia constant. In Table 4 are given data on a series of 5 Cæsarean sections, all performed on multiparæ. The anesthetic in all cases was nitrous oxide and ether, and the time given is that from the start of anesthesia to delivery, when determinations were made.

TABLE 4.—DATA ON CÆSAREAN SECTIONS.

Case No.	Fasting blood sugar, mg./100 cc.	Delivery blood sugar, mg./100 cc.		Duration of anesthetic, min.	Pre-operative medication.
		Maternal.	Infant.		
42 . . .	91.5	110.2	71.1	25	Pentabarb., gr. iij.
33 . . .	102.2	116.3	95.8	15	Sodium amytal, gr. iij.
2 . . .	..	117.0	104.6	15	Sodium amytal, gr. iij.
72 . . .	87.3	117.7	89.8	25	Sodium amytal, gr. vj.
89 . . .	96.5	121.7	84.2	23	Sodium amytal, gr. iij.
Mean . .	..	116.6	89.1	21	

In this series, the duration of anesthetic is less varied than in any 5 consecutive routine cases, and the range of the maternal blood sugar is distinctly more compact, all falling within the 12 mg. range from 110 to 122 per 100 cc. The mean maternal blood sugar is 116.6, significantly lower than 124.6, the mean of the 50 routine cases. Likewise the mean of 89.1 for these 5 infants is significantly lower than 103.6, the mean for 47 infants in the routine series.

To determine the effect of labor alone 2 patients were delivered by local perineal block with novocaine, which is known to have no effect on the blood sugar. Both of these patients were primiparæ on the morphine and scopolamine medication as previously outlined, and delivery was effected in both cases by low forceps, with episiotomy (Table 5).

TABLE 5.—DATA ON PERINEAL BLOCK CASES.

Case No.	Delivery blood sugar, mg./100 cc.		Labor, hours.		Medication.	Notes.
	Maternal.	Infant.	Total.	Second stage.		
62 . . .	106.1	66.0	21:35	:35	M&S	Novocaine, 50 cc.
67 . . .	114.4	85.5	9:05	:55	M&S, amyt.	Novocaine, 60 cc.
Mean . .	110.3	75.7				

The mean maternal blood sugar is 110.3, and that of the infants, 75.7, when labor alone is permitted to operate. Both of these are significantly lower than the means for routine deliveries.

From Tables 4 and 5 it seems that elimination of either labor or anesthesia produces a rise in blood sugar less than that obtained when both of these factors enter the picture.

A Cæsarean section under local anesthesia eliminated both labor and inhalation anesthesia. This patient, a 23-year-old primipara, had rheumatic heart disease. Pre-operative medication consisted of sodium amytal, grains, vj; novocaine, 1%, was used to effect anesthesia. The maternal blood sugar at delivery was 68.8 mg. per 100 cc., and that of the infant, 65.2. This is lower than any maternal blood sugar found in Tables 3, 4 and 5; thus when anesthesia and labor are both eliminated it would seem that the blood sugar remains within normal range.

From the application of the Pearson rank-order correlation formula to the data presented in Table 3, and from the foregoing data, we feel justified in concluding that labor and anesthesia, alone or combined, cause a rise in the level of the blood sugar at delivery, but it appears that the duration of these factors is not of primary importance in determining the final level attained. Obviously such factors as the rate of excretion of insulin and adrenalin, the severity of labor, available glycogen stores, and the effect of previous diet[5] cannot be overlooked in an analysis of the subject. The interchanging influence of these constituents cannot be evaluated by any research methods now at our disposal. In addition, it has been shown that the blood sugar of the infant is dependent upon that of its mother; factors raising the maternal blood sugar cause a corresponding, but generally smaller, rise in the infant.

TABLE 6.—SUMMARY OF DATA ON BLOOD SUGAR AT DELIVERY.

Type of delivery.	Number of cases.	Mean blood sugar, mg./100 cc.	
		Maternal.	Infant.
Routine forceps delivery	50 maternal 47 infant	124.6	103.6
Cæsarean section, GOE, no labor	5 maternal 5 infant	116.6	89.1
Forceps delivery, local, labor	2 maternal 2 infant	110.3	75.7
Morriss, normal, spontaneous, chloroform	28 maternal 24 infant	132.0	115.0
Holman and Mathieu,[1] normal, no other data given	100 maternal 100 infant	100.5	95.4
Cæsarean section, local, no labor	1 maternal 1 infant	68.8	65.2

Table 6 summarizes the blood-sugar values for our cases of various types, and those obtained by Morriss, and Holman and Mathieu. Allowing for the difference in values obtained by the tests used, it is seen that we have verified the work of Morriss. This is interesting in view of the great difference in obstetrical technique, and implies that the blood-sugar values at delivery are not greatly altered by the changes in management of obstetrics.

In 28 of our cases, the blood sugar during the first stage was compared with that at delivery. These data are tabulated in Table 7, which shows the dilatation by rectal examination at the time of the determination, the delivery blood sugar, and the hours prior to delivery. In every case the blood-sugar value at delivery was higher than during the first stage. There is a tendency for patients showing a high degree of cervical dilatation to present blood-sugar values above normal (50% of patients showing blood sugars over 100 are 4 times or more dilated) while with little or no dilatation patients tend to present values in the normal range. The mean for these 28 cases in the first stage is 93.4, a figure doubtless somewhat raised due to the number of determinations made late in the first stage. The mean blood sugar at delivery is 121.8. We believe the character of the rise in blood sugar during labor needs further study, and therefore reserve for a later date more detailed reports on this phase of the subject.

TABLE 7.—COMPARISON OF BLOOD SUGAR DURING THE FIRST STAGE AND AT DELIVERY.

Case No.	Dilatation at time of determination.	Blood sugar, mg./100 cc. During first stage.	Blood sugar, mg./100 cc. At delivery.	Hours before delivery.
73	1 ×	66.2	98.4	3:30
83	4 ×	76.3	102.5	3:00
90	2 ×	78.9	110.0	3:45
46	4 ×	80.5	104.5	3:20
21	1 ×	80.6	135.5	3:45
38	2–3 ×	82.5	103.0	3:50
69	2 ×	84.0	121.8	6:45
61	4 ×	84.3	117.7	3:05
64	Rim	85.4	110.2	6:15
56	None	86.3	116.8	3:00
70	4 ×	86.9	124.8	3:55
74	2 ×	87.1	130.4	7:05
58	2 ×	89.8	114.8	4:07
24	2–3 ×*	90.8	106.6	5:50
87	3 ×	90.9	100.2	3:25
47	3 ×	93.1	124.2	4:00
26	4 ×	96.0	107.4	1:40
63	Rim	100.4	107.5	1:00
13	Rim	100.4	122.5	1:10
80	1 ×	103.0†	133.9	9:45
35	Finger tip	103.7	139.5	4:45
59	Rim	105.8	153.0	2:50
37	1½ ×	106.1	108.8	8:07
29	2 ×	108.2	187.4	7:00
86	4 ×	109.4	136.9	2:45
65	1½ ×	112.6	128.0	7:30
30	Rim	113.2	137.3	2:50
68	2 ×	115.0	127.5	6:10
Mean	...	93.4	121.8	

* Estimated.

† Taken short time after light meal; not yet returned to fasting; not included in percentages.

Comparison of the blood sugar during the first stage with that of the puerperium has had relatively little investigation. Rowley[6] found a mean of 110 mg. per 100 cc. in 53 cases of pregnancy at term, and a mean of 140 mg. per 100 cc. in 22 cases 2 days postpartum, using the Lewis-Benedict method; apparently these determinations are on different individuals. Morriss, in investigating this phase, likewise did not compare the same individuals during labor and the puerperium, but concluded from determinations on 10 individuals made at varying times postpartum that the blood sugar was slightly higher than normal.

TABLE 8.—COMPARISON OF BLOOD SUGAR VALUES DURING THE FIRST STAGE WITH THAT OF SECOND OR THIRD DAY POSTPARTUM.

Case No.	Dilatation of cervix at time of first stage.	Blood sugar, mg. per 100 cc.		
		During first stage.	2 or 3 days postpartum.	At delivery.
73	1 ×	66.2	97.5	98.4
77	2 ×	74.8	92.8	147.8
83	4 ×	76.3	86.1	102.5
90	2 ×	78.9	97.2	110.0
46	4 ×	80.5	76.2	104.5
38	3 ×	82.5	96.8	103.0
69	2 ×	84.0	84.0	121.8
56	0	86.3	86.4	116.8
70	4 ×	86.9	82.1	124.8
74	2 ×	87.1	78.2	130.4
58	2 ×	89.8	94.7	114.8
87	3 ×	90.9	114.9	100.2
47	3 ×	93.1	84 9	124.2
75	2 ×	97.2	91.2	112.6
63	Rim	100.4	104.8	107.5
80	1 ×	103.0*	82.1	133.9
35	1½ ×	103.7	92.7	139.5
37	1½ ×	106.1	86.6	108.8
86	4 ×	109.4	99.0	136.9
91	4 ×	110.0	63.8	130.5
65	1½ ×	112.6	113.9	128.0
30	Rim	113.2	97.7	137.3
68	2 ×	115.0	73.0	127.5
Mean		93.4	90.3	120.1

* Taken short time after meal; not yet returned to fasting.

Table 8 presents blood-sugar values on 23 patients during the first stage and puerperium. Postpartum blood sugars, either fasting or 4 hours following a light breakfast, were obtained on the second or third day following delivery.

The mean first stage blood sugar in this series was 93.4; the mean postpartum blood sugar, 90.3; the mean blood sugar at delivery, 120.1. The blood sugar at delivery, therefore, represents a temporary rise. It might seem from the mean values that the postpartum blood sugar does not differ widely from that of the first stage of labor. However, inspection of the table shows that, during the first stage, 47.8% of these women had blood sugars above the range for normal adults, and consequently it may be assumed that the level has been influenced by labor. With 2 exceptions, the 11 women having blood sugars higher than the normal range showed a fall in the puerperium. Of the 12 women showing first-stage blood sugars lower than 90 mg.

per 100 cc., 6 show higher values during the puerperium, 5 show approximately the same values and 1 is lower. We conclude that the blood sugar 2 or 3 days postpartum is slightly higher than normal for the individual.

Having followed the mothers into the puerperium, it seemed logical to follow the newborns during the first few days of life. Table 9 gives results of determinations on 37 individual babies at delivery and for 3 consecutive days. The data shows that there is a definite drop in blood sugar during the first 24 hours of life, since the mean delivery blood sugar on these 37 infants was 103.8, and the mean for the first day of life, 67.4. The mean for the second day is 70, practically the same as that of the first day. On the third day there is a slight rise in mean to 75.5. Fifty-nine and a half per cent of the babies show a rise on the second or third day over the first.

TABLE 9.—BLOOD-SUGAR DETERMINATIONS ON NEWBORNS FOR 3 SUCCESSIVE DAYS

Case No.	Blood sugar at delivery.	Blood sugar first day.	Blood sugar second day.	Blood sugar third day.
26	86.4	46.6	59.6	60.8
68	106.1	53.8	60 8	69.2
56	78.2	55.1	70.0	61.8
43	..	55 7	52.4	83.6
44	72.3	56 0	73.5	78.5
46	74.1	56 2	79.5	75.8
5	77.2	58.8	75.2	83.0
7	135.7	60.3	64.5	82.3
41	86.4	61.4	65.7	81.4
49	84.7	61.8	67.0	79.1
58	97.4	62.5	71.6	75.2
69	99.5	62.6	66.2	68.1
45	84.0	63.5	62.4	69.9
12	99.0	64.2	68.9	90.9
54	88.6	64.4	70.0	76.2
55	103.8	65.0	63.9	64.2
6	78.0	65.1	71.5	81.4
47	117.0	66.2	69.7	83.3
36	115.4	68.5	66.2	72.0
38	95.7	68.8	65.0	63.4
22	87.7	69.2	65.0	78.6
65	116.1	70.0	63.0	70 0
37	95.3	70.1	63.9	66.6
70	102.7	70.4	82.3	67.6
28	114.7	71.1	79.1	78.5
60	151.8	72.3	70 6	78 0
66	105.0	73.1	74.5	72.7
64	93.8	74.3	57.4	74 1
34	122.2	74.9	77 1	73 3
59	126.1	75.3	70.2	72 9
39	121.9	75.8	78.5	93.6
9	105.0	76.1	74.8	73 3
8	122.9	76.1	68.3	65 3
11	136.3	78.5	63 2	79.4
30	104.8	80.5	83 8	83.0
51	86.6	82.4	71.3	84.4
10	161.6	87.0	102 9	81.4
Mean	103.8	67.4	70.0	75.5

Blood-sugar collections were made 3½ to 4 hours after feedings.

Using the 37 cases above and adding further cases not necessarily consecutive but falling on the first, second or third day we have established the normal values for newborns with the Folin-Malmros technique (Table 10).

TABLE 10.—FREQUENCY DISTRIBUTION OF BLOOD-SUGAR VALUES IN NEWBORN.

Blood-sugar value, mg./100 cc	Number at each age. At birth.	3 to 6 hours.	First day.	Second day.	Third day.
45– 54.9	0	0	2	1	0
55– 64.9	0	4	16	10	5
65– 74.9	1	4	17	21	14
75– 84.9	8	2	7	8	20
85– 94.9	7	0	2	0	2
95–104.9	9	0	1	1	0
105–114.9	9	0	0	0	1
115–124.9	8	0	0	0	0
125–134.9	1	0	0	0	0
135–144.9	2	0	0	0	0
145–154.9	2	0	0	0	0
Total cases	47	10	45	41	42
Mean (mg./100 cc.)	103.6	66.8	68.3	70.3	76.1
Normal range	..	55–75	55–75	55–75	65–85
Highest value of series		79.1	102.2	102.9	110.3
Lowest value of series		56.9	46.6	52.4	57.1

Blood-sugar collections were made 3½ to 4 hours after feedings.

Table 10 shows a drop from the high values at birth to a mean value of 66.8 during the first 3 to 6 hours. The mean values 3 to 6 hours after birth, and on the first and second day are practically the same; on the third day there is a small but appreciable rise. There is also a rise in the normal range. The lowest blood sugar of the series, 46.6, was not attended by clinical signs of hypoglycemia. We conclude, therefore, that the normal blood-sugar values for newborns by the Folin-Malmros technique is somewhat lower than the normal values for adults, and lies between 55 and 75 mg. per 100 cc. for the first 2 days of life with slightly higher values later.

Conclusions. 1. The Jeghers-Myers modification of the Folin-Malmros micro method for blood sugar is an accurate and practical test for use with adults and newborns; 85% of the duplicates check within 3%.

2. The mean maternal blood sugar at delivery in 50 cases was 124.6, with 60% of the cases falling between 110 and 140 mg. per 100 cc., approximately 40 to 50 mg. above the normal range.

3. The mean blood sugar for 47 infants at birth was 103.6; 94% of these infants presented values lower than those of their respective mothers.

4. Both anesthesia and labor have been shown to contribute to the rise in blood sugar at delivery, but there is no indication that the duration of these factors is the primary cause of the rise.

5. The blood sugar of the infant is dependent upon that of its mother, and factors affecting the blood sugar of the mother affect that of the infant.
6. Taking into account the method used in determining blood-sugar values, we have confirmed the work of Morriss (1917). Inasmuch as the management of labor and delivery is entirely different in the two series, it would seem that the newer obstetrical techniques produce no deleterious effects on the glucose metabolism.
7. In 28 cases, comparison showed the blood sugar higher at delivery than during the first stage by a difference in mean of 28 mg. per 100 cc.
8. The blood sugar of any particular individual 2 or 3 days postpartum is somewhat higher than normal.
9. We have established the normal blood-sugar range for newborns by the modified Folin-Malmros technique. The first 2 days of life the blood sugar is 55 to 75 mg. per 100 cc., with slightly higher values on the third day.
10. Within 3 to 6 hours after birth the blood sugar drops to the normal infant range.

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THE BLOOD AND URINE OF DOGS FOLLOWING PARALDEHYDE.

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Judging from the meager amount of information which appears in the literature,[2,11] little is known of the changes which occur in certain constituents of the blood and urine following the administration of paraldehyde. Since this drug has assumed renewed importance in recent years, particularly in the field of obstetrics,[4,6,7,9,10] it was felt that additional studies of this nature were necessary.

Our first investigations were concerned with the effects produced by paraldehyde on the amounts of fermentable and non-fermentable reducing substances of the blood, by means of which for the first time, so far as is known, the changes which occurred were definitely identified as being due to glucose fluctuations. Later these investigations were extended to include the urine. When it became apparent that the blood showed an increased viscosity during the anesthetic stages, and clotted more readily, changes in the red cell volume were studied by hematocrit determinations, since blood volume changes might affect the blood sugar content.[12] The carbon dioxide combining capacity of the blood plasma was also studied during the course of several experiments, to determine the extent of changes in the acid : base balance, which have been observed to occur with other anesthetics.

Experimental Procedure. The animals used were healthy adult dogs, weighing 7 to 17 kgs. They were fed *ad libitum* on a brand of prepared dog food, occasionally supplemented with raw meat and cod-liver oil. All food was removed 18 hours before experimental procedures were begun. The experiments were usually continued for 6 hours, samples of venous blood and catheterized urine being obtained at hourly intervals. Clotting was prevented by the addition of 2.5 mg. of powdered potassium oxalate per cc. of blood, the minimum amount found necessary for this purpose.

The normal average daily variation of the blood sugar level was determined three times at weekly intervals on each of 6 dogs from samples removed during the 6-hour period at 9.00 A.M., 12.00 M., and 3.00 P.M. In the case of the experimental animals, after control samples of blood and urine had been obtained, an anesthetic dose of paraldehyde, usually 1.8 cc. per kg.,[5] was administered either by stomach tube or slowly by rectum. When given by the latter route the rectum was first emptied by irrigation, and 1.5 cc. of benzyl alcohol was mixed with the paraldehyde to minimize local irritation.[6] The animal was held in a prone position until there was no danger of loss of the drug from the rectum; in no instance did vomiting occur following gastric or rectal administration.

The majority of the experiments were conducted at room temperature, with the animals covered sufficiently to avoid excessive loss of body heat. In those tests where the effects of moderate extremes of temperature were also investigated, heat was supplied by electric heating pads, and cold by exposure to cold air from an open window, such measures being initiated 1 hour after paraldehyde had been given, and the animals were quiet.

The total amount of reducing substances in the blood was determined by the method of Benedict;[3] the non-fermentable reducing substance was estimated by the same procedure after yeast fermentation. The methods used for determining these substances in the urine were identical except that dilution of the urine from 60 to 80 times was necessary, depending on the concentration of reducing substances and pigment present in the particular sample.

The red cell volume (hematocrit) determinations were made by centrifuging the freshly oxalated blood in glass tubes sealed at one end, until no further settling occurred. For this purpose pieces of glass tubing 7 cm. in length with an inside diameter of 1½ or 2 mm. were used, a small drop of mercury being placed in the sealed end to fill the tapering bore and give a uniform meniscus. Readings were obtained with a millimeter rule and magnifying glass. Although the use of oxalate causes a slight shrinkage of the red cells[8] resulting in a slightly smaller volume reading, this can be disregarded since it is constant in each test.

While it is obvious that there is no exact method of measuring the degree of hypnosis or anesthesia, the following symptomatic classification appeared to give a fair evaluation, and served satisfactorily as a basis for construction of the "anesthesia curves" shown in the figures. Induction stage: animal awake, either standing or reclining, muscular incoördination, quiet or struggling. Light anesthesia: animal asleep, but awakens when needle penetrates the skin. Complete anesthesia: animal unconscious, breathing slow, deep and regular, reflexes active, does not react to needle puncturing the skin.

Results. *Effect of Paraldehyde on the Blood Sugar Level.* The maximum fluctuation of the blood sugar levels of 6 fasting control dogs over the 6-hour period averaged about 7 mg. %, and never exceeded 10 mg. % in any one animal in the control tests on 18 separate days.

Since 1.5 cc. of benzyl alcohol was always mixed with paraldehyde when the latter was given by rectum, it was first necessary to determine whether or not the former had any effect on the blood sugar level. Hourly fluctuations which occurred in such experiments on 2 dogs were so slight and inconstant as to be of no significance, so that benzyl alcohol need not be considered as a factor in the production of these changes.

TABLE 1.—THE BLOOD SUGAR LEVEL FOR 6 HOURS AFTER PARALDEHYDE.

Dog No.	No. of tests.	Paraldehyde.		Blood sugar (mg. %).						
		Amount (cc. per kg.).	Route— "r": rectum. "s": stomach.	Control.	Hours after administration.					
					1.	2.	3.	4.	5.	6.
37 . . .	5	1.7	5 r	76	92	83	81	82	76	85
38 . . .	4	2.7	3 r, 1 s	63	73	73	77	79	78	67
39 . . .	3	1.5	3 r	67	77	72	70	73	72	65
55 . . .	7	1.8	4 r, 3 s	72	93	79	78	70	70	73
63 . . .	2	1.8	2 s	77	120	106	97	93	95	93
65 . . .	1	1.8	1 s	66	74	83	89	94	96	80
66 . . .	7	1.8	3 s, 4 r	79	88	78	74	75	77	79
72 . . .	1	1.8	1 s	75	111	136	167	154	139	128
75 . . .	6	1.8	2 s, 4 r	73	91	83	79	96	96	88
88 . . .	3	1.8	3 r	72	77	78	81	84	82	79
98 . . .	5	1.8	5 r	78	105	111	108	109	108	102
99 . . .	4	1.8	4 r	71	76	77	81	87	78	78
Totals . .	48	...	13 s, 35 r	...	...	...	...	...	...	...
Average .	...	1.8	.....	73	89	84	84	85	84	82

The administration of 1.8 cc. of paraldehyde per kilogram of body weight by stomach or by rectum produced a small average rise of the blood sugar level in 48 experiments on 12 animals (Table 1). The rise averaged 16 mg. % at the end of the first hour, and maintained an average increase of 11 mg. % above normal during the remaining 5 hours of observation. Some individual variations from the average blood sugar level occurred, such as secondary rises, falls below normal after a preliminary rise, and slow progressive elevations. These variations which perhaps depend to some extent upon individual reaction to the drug, are probably due mainly to differences in the rate of its absorption, since the blood sugar level in some instances varied considerably in character in the same animal on different days. The maximum rise of the blood sugar level generally occurs during the partial development of anesthesia in the first hour; a slight fall occurs during the second hour as the anesthetic effect reaches its maximum, and the lower level which is maintained during the remaining 4 hours parallels the anesthetic effect.

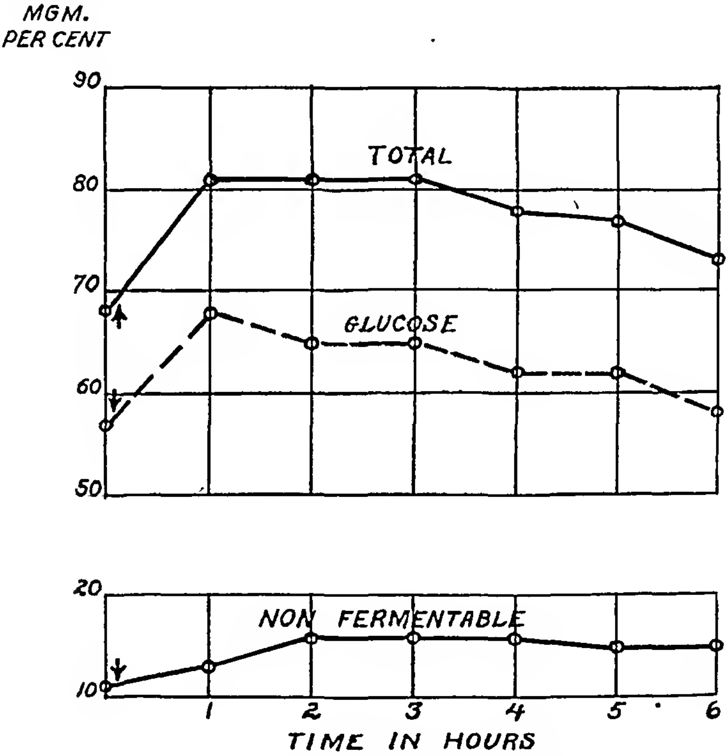

FIG. 1.—Total, fermentable and non-fermentable substances in the blood of dogs following paraldehyde (1.8 to 4 cc. per kg.). (↑ = paraldehyde administered.)

Partition of Reducing Substances in the Blood Under Paraldehyde. Early in our investigations it was found that the Benedict reagent is reduced by paraldehyde, and since it was possible that sufficient amounts of the latter might be present in the blood to partially account for the reduction obtained, simultaneous determinations of the total and non-fermentable reducing substances in the blood were made in 6 experiments following paraldehyde, using the yeast fermentation technique described above. Even though larger amounts of paraldehyde were administered than usual, it was found that the fluctuations in the amount of non-fermentable reducing substance were insufficient to account for the changes in the reducing power of the blood (Fig. 1). It can therefore be concluded that these changes were due to variations in the amount of glucose, and not to other non-fermentable reducing substances, or to paraldehyde.

The Relation of External Temperature to the Blood Sugar Level Under Paraldehyde. While most of our experiments were performed at room temperature, the results of the investigations reported in Table 2 on 6 dogs are from tests designed to determine what influence, if any, was exerted by external temperature on the blood sugar level after paraldehyde. In experiments at room temperature it had been observed frequently that after receiving this drug some of the animals exhibited trembling movements even when well covered; it was therefore felt necessary to determine whether these were shivering movements due to thermal conditions, or muscular movements brought about by some other action of the drug, and what was their effect on the blood sugar level. Accordingly, two experiments were performed on each of 6 animals; in one test the animal was kept warm with electric pads and blankets, the temperature being held just low enough so that the animal would not pant;[1] in the other test it was uncovered and exposed to the

TABLE 2.—INFLUENCE OF TEMPERATURE ON THE BLOOD SUGAR LEVEL FOLLOWING PARALDEHYDE (1.8 CC. PER KG., RECTALLY).

Dog No.	No. of tests.	Blood sugar (mg. %).							External temperature.*
		Control.	Hours after administration.						
			1.	2.	3.	4.	5.	6.	
55 . .	1	65	78	59	64	48	53	70	High
	1	69	87	72	70	65	50	49	Low
66 . .	1	76	98	78	78	83	77	81	High
	1	76	84	74	70	74	76	79	Low
75 . .	1	75	106	93	78	86	84	82	High
	1	73	87	78	74	96	86	88	Low
88 . .	1	64	67	71	76	(animal awake)			High
	1	72	78	81	85	84	82	89	Low
98 . .	1	71	159	149	128	111	106	95	High
	1	80	90	146	154	137	127	115	Low
99 . .	1	68	79	76	77	74	60	70	High
	1	72	76	82	77	85	82	79	Low
Averages of 6 high		70	98	88	83	80	76	80	
Averages of 6 low		74	84	89	88	91	84	82	

* Second to sixth hour, inclusive.

winter cold in front of an open window at temperatures ranging −1 to +13°C. and averaging 6° C., so that it shivered violently throughout the experiment. These procedures were employed just after the blood (and urine) samples had been taken at the end of the first hour following the administration of paraldehyde, so that the results in Table 2 are significant in respect to temperature influence beginning with the second hour only.

While the average results indicate that the blood sugar level under paraldehyde was slightly higher when the animal was exposed to cold than when kept warm, this was true in only half of the experiments. Trembling was also observed in some of the animals which were kept warm. It would therefore appear that the room temperatures at which most of the tests were performed were entirely satisfactory, the blood sugar changes after paraldehyde not being attributable to variations in room temperature. It also seems apparent that the trembling movements are primarily induced by some other action of paraldehyde than lowering of temperature, since they occurred at times when the animals were warm, and often were absent when the tests were run at room temperature. However, these trembling movements were either intensified or changed into shivering movements when the animals were exposed to low temperatures.

Abnormal Elevation of the Blood Sugar Level in a Poorly Nourished Dog Under Paraldehyde. The results obtained on Dog 98 are interesting because of the unusually high elevations of the blood sugar level which occurred under paraldehyde when this animal was in a poorly nourished condition (Table 3). These marked increases occurred in the first 3 experiments when the animal was very thin, but otherwise apparently normal, similar results being obtained even under opposing extremes of external temperature. After the animal had gained weight the small changes in the blood sugar level

TABLE 3.—ABNORMAL ELEVATION OF THE BLOOD SUGAR LEVEL OF A POORLY NOURISHED DOG (NO. 98) FOLLOWING PARALDEHYDE (1.8 CC. PER KG. RECTALLY).

Date.	Weight (kg.).	Blood sugar (mg. %).							External temperature.*	Condition.
		Control.	Hours after administration.							
			1.	2.	3.	4.	5.	6.		
12/22/36	10.7	75	76	75	85	108	121	125	Room	Thin
1/15/37	11.0	71	159	149	128	111	106	95	High	Thin
2/4/37	11.0	80	90	146	154†	137†	127	105	Low	Thin
3/29/37	14.3	82	94	91	81	78	82	86	Low	Robust
5/7/37	15.0	82	105	96	94	111	106	99	Room	Robust

* Second to sixth hour, inclusive.
† Glycosuria occurred.

under paraldehyde approximated those obtained in the other normal animals. No abnormal conditions were found at autopsy when the animal was sacrificed after the last experiment. Sugar occurred in the urine in the third experiment only, at blood sugar levels slightly lower than in the preceding experiment where this event did not occur.

The Amount of Reducing Substances in the Urine Under Paraldehyde. The amount of non-fermentable reducing substances in the urine following paraldehyde administration showed a progressive increase during the 6-hour period in the 13 tests performed on 6 animals (Table 4). Fermentable reducing substance (glucose) was present in only 1 experiment. Since the Benedict reagent is reducible by paraldehyde, it appears probable that the latter forms part of the non-fermentable reducing substances, and that its excretion may largely account for the increased reducing power of the urine.

TABLE 4.—THE AMOUNT OF REDUCING SUBSTANCE IN THE URINE FOLLOWING PARALDEHYDE (1.8 CC. PER KG., RECTALLY).

No. of animals.	No. of tests.	Reducing substance (in mg.).							Type.
		Control.	Hours after administration.						
			1.	2.	3.	4.	5.	6.	
6 . . .	13	25	44	58	68	127	135	101	Non-fermentable
1 . . .	1	. . .	. .	. .	59*	249*	. . .	. .	Fermentable (glucose)

* Glucose present in urine in one experiment on 1 animal (Dog 98).

The concentration as well as the amount of non-fermentable reducing substances in the urine showed a progressive increase, since the rate of urine output remained about the same over the 6-hour period.

Effect of Paraldehyde on the Red Cell Volume (Hematocrit). Hematocrit determinations in 24 experiments on 6 dogs (Fig. 2) revealed a 3% decrease in the red cell volume in the first hour following paraldehyde. The red cell volume then increased progressively until it was 3% above normal at the end of the fourth hour, and declined toward normal in the last 2 hours as anesthesia lessened. The red cell volume apparently is unrelated to the blood sugar curve.

Effect of Paraldehyde on the Carbon Dioxide Combining Capacity of the Blood Plasma. The carbon dioxide combining capacity of the blood plasma was determined in 5 experiments on different animals following paraldehyde administration (Fig. 3). The results obtained on Dog 99 are plotted separately, since this animal showed only slight hypnotic effects, mainly during the first and second hours, due to loss of some of the drug from the rectum, and had almost entirely recovered by the end of the experiment.

The carbon dioxide combining capacity decreased progressively during the first 5 hours and began to recover during the last hour, in the 4 experiments where good anesthesia occurred. In Dog 99 the decrease in this property was much less marked, with an earlier recovery.

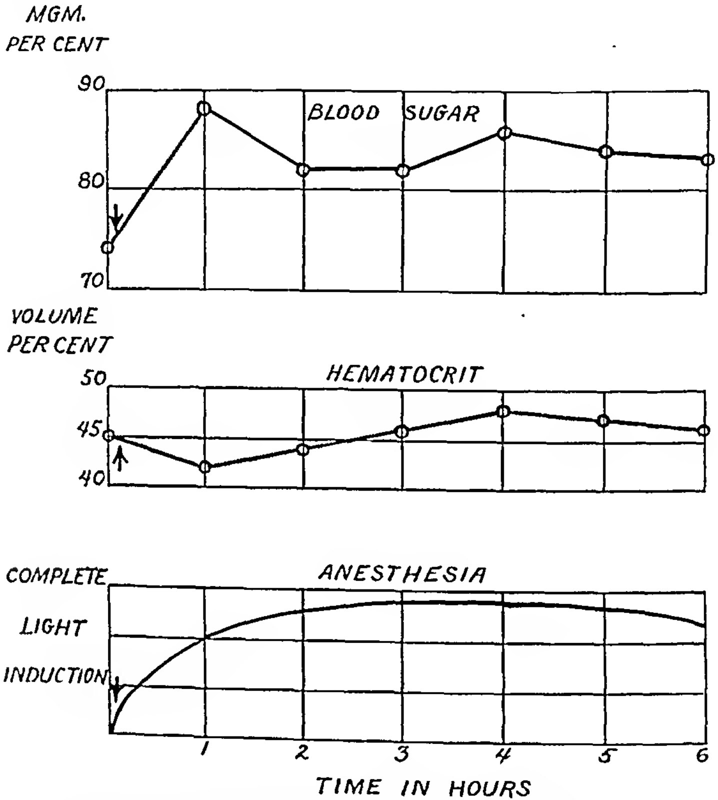

Fig. 2.—The red cell volume (hematocrit) and the blood sugar level of dogs following paraldehyde (1.8 cc. per kg.). (↑ = paraldehyde administered.)

The hematocrit curves included in the chart indicate that the usual changes in red cell volume occurred only during good anesthesia. Changes in both the red cell volume and carbon dioxide combining capacity were smaller and less constant in the experiment on Dog 99 in agreement with the brief and mild hypnotic effect.

Discussion. While numerous investigators have shown that anesthesia produced by ether, chloroform, nitrous oxide and ethylene is accompanied by a rise in the blood sugar level and a reduction in the plasma bicarbonate, the results reported on similar studies on the large group of barbiturates are often quite contradictory, and a search of the literature has revealed only two such references on paraldehyde. Sollmann[11] states that Powell, in 1914, found hypnotic doses of paraldehyde lowered the blood sugar level in dogs, while anesthetic doses produced considerable hyperglycemia and glycosuria. Beauchemin, Springer and Elliott[2] recently reported that 5 to 19 cc. of paraldehyde, rapidly injected intravenously in human insane patients, produced good anesthesia lasting 1½ to 21 minutes, accompanied by hyperglycemia (maximum of 30 mg. %) which began to fall after 1 hour, and disappeared by the end of 24 hours.

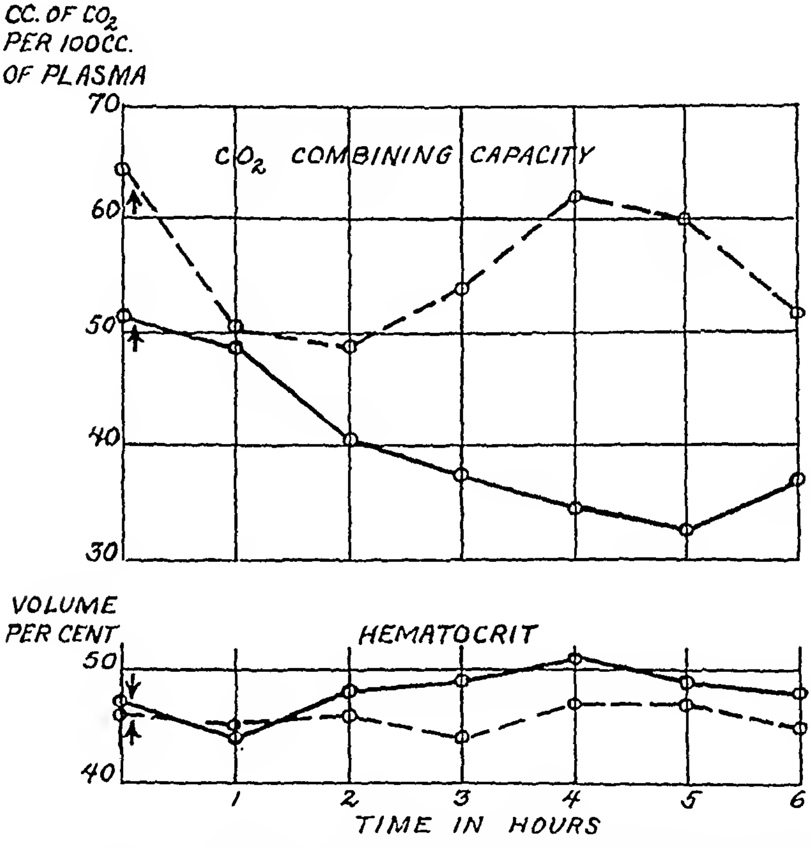

FIG. 3.—The carbon dioxide combining capacity of the plasma and the red cell volume of the blood of dogs following paraldehyde (1.8 cc. per kg.). (Broken line, Dog 99, mild hypnosis only. Solid line, average of Dogs 55, 66, 75, 98, good anesthesia. ↑ = paraldehyde administered.)

The relatively small elevations of the blood sugar level which occurred in our experiments on dogs with paraldehyde, as compared to those obtained by numerous investigators with various other anesthetics, can probably be accounted for on the basis of milder anesthetic activity and slower action of this drug. The results of our investigations do not confirm those ascribed to Powell above, since our anesthetic doses produced only a mild hyperglycemia, and no glycosuria in healthy normal animals. In the one experiment where only light hypnosis was obtained due to loss of the drug from the rectum (Dog 99), the elevation of the blood sugar level was similar in degree to that which followed the anesthetic dose.

In our experiments there was relatively little excitement or struggling during the induction of anesthesia; during the anesthetic stage there were only moderate changes in the respiration, neither hyperpnea nor dyspnea occurring. The possible effects of extremes of external temperature, through stimulation of muscular tone and activity (shivering) and stimulation of respiratory activity (panting) have been shown to be unimportant in regard to changes in the blood sugar level under paraldehyde in these experiments.

There was a gradual decrease in the carbon dioxide combining capacity of the blood plasma from the first to the fifth hour, with a slight return to normal in the fifth to sixth hour. These findings indicate that a mild to severe acidosis was produced according to the classification of acidosis by Van Slyke.[13]

The primary decrease in red cell volume in the induction of paraldehyde anesthesia, followed by an increase in the anesthetic stage, is the reverse effect to that which occurred in the blood sugar level. It therefore appears that the changes in blood sugar level observed were not due to variations in the red cell volume.

Summary. 1. The gastro-enteral administration of anesthetic doses of paraldehyde (1.8 cc. per kg.) to healthy fasting dogs produced a small but definite average elevation of the blood sugar level. In general, this elevation was greatest during the first hour, averaging 16 mg. %; during the remaining 5 hours a level which averaged 11 mg. % was maintained. Occasionally the level approached or fell below normal during the later hours; in some cases a secondary rise occurred, while in others the rise was delayed and continued throughout the experiment.

2. By means of yeast fermentation technique it was definitely ascertained that the elevations in the reducing substance of the blood observed under paraldehyde were entirely attributable to increases in the amount of glucose.

3. A small amount of benzyl alcohol (1.5 cc.), administered rectally with paraldehyde to minimize the irritating effect of the latter, had no effect on the blood sugar level; nor was the character of the blood sugar level under paraldehyde altered by moderate extremes of cold and warmth in the external temperature.

4. High elevations of the blood sugar level (50, 78 and 74 mg. %) occurred in a thin and poorly nourished animal under paraldehyde anesthesia; however, when the animal had gained weight and was in good condition, the usual small increases in blood sugar were obtained under the same procedure.

5. Glycosuria did not occur in normal dogs during paraldehyde anesthesia, nor were there significant quantitative changes in the rate of urine secretion. There was, however, a marked progressive increase in the amount of non-fermentable reducing substance in the urine, the nature of which was not determined, but which is suspected of being paraldehyde or its decomposition products.

6. The red cell volume (hematocrit) of the blood showed an average decrease of 3% at the end of the first hour following paraldehyde, then rose progressively to a maximum of 3% above normal in the fourth and fifth hours, returning to normal by the end of the sixth hour.

7. The carbon dioxide combining capacity of the blood plasma during paraldehyde anesthesia was lowered to a degree corresponding to moderate to severe acidosis (32.5 cc. per 100 cc. of plasma).

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OBSERVATIONS ON TWO DIFFERENT PRESSOR SUBSTANCES OBTAINED FROM EXTRACTS OF RENAL TISSUE.*

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Since the time of Bright most clinicians have believed that certain disorders of the kidney may lead to an increase in blood pressure. This concept has recently received experimental support from the work of Goldblatt[7] and his colleagues, who have shown that partial obstruction of the renal arteries produces hypertension in dogs, an observation which has been confirmed by Page,[16] Friedman and Prinzmetal,[6] and others.[4,9] Hartwich[11] observed increase in blood pressure following ligation of the ureters. His results are confirmed by Harrison *et al.*,[10] who failed to obtain comparable increase in blood pressure after bilateral nephrectomy, and concluded that the development of hypertension was dependent in some manner on the presence of malfunctioning renal tissue in the body and was not related to failure of the renal excretory mechanism.

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* This study was aided by a grant from the Division of Medical Sciences of the Rockefeller Foundation.

The "renal" hypertension occurring under the conditions mentioned above might be the result either of a reflex initiated in the kidneys or of some chemical substance elaborated in these organs. That the former hypothesis cannot be correct is indicated by the experiments of Page,[16] Elaut[4] and of Collins,[2] who showed that denervation of kidneys did not prevent the rise in blood pressure following the application of a Goldblatt clamp to the renal arteries, and Harrison and his coworkers, who found that ligation of the ureters caused a rise in blood pressure regardless of renal denervation. By exclusion, it seems that "renal" hypertension is dependent on the pressor effects of some chemical agent elaborated in the kidney. Attempts to demonstrate such a substance in the blood of hypertensive animals have led to conflicting results. Govaerts and Dicker[5] obtained positive effects while negative findings have been reported by Friedman and Prinzmetal[6] and Page.[16] On the other hand, pressor effects from the kidneys of hypertensive animals have been reported by Hartwich,[11] Harrison, Blalock and Mason,[9] and by Friedman and Prinzmetal.[6] These authors, dealing with renal saline extracts, obtained greater pressor effects from the kidneys of hypertensive than from normal animals. However, since these extracts also had well-marked depressor effects, the findings were not entirely convincing and it was felt that the experiments should be repeated with extracts freed from confusing depressor substances. The observations to be reported in the present paper deal with attempts to purify the pressor principle of renal extracts.

In 1898, Tigerstedt and Bergman[22] reported that the intravenous administration of saline extract of rabbits' kidneys to other rabbits caused a 10 to 50% rise in blood pressure, which came on slowly and had a long duration. The active substance, which they called "renin," was non-dialysable, and heat labile. It was found chiefly in the cortex of the kidney, and was still effective after cervical chordotomy and vagal section. These findings, while not completely confirmed by some authors,[15,18] have been substantiated by Bengel and Strauss[1] and Thauer,[21] and Hartwich and Hessel.[12,13] Bengel and Strauss obtained "renin" from renal press-juice rather than from saline extract. They concluded that it was soluble in water, non-dialysable, precipitable by ammonium sulphate in proper concentration and seemed to be a protein. Hessel and Hartwich, working with autolyzed press-juice, confirmed the results of Bengel and Strauss. However, they found that when autolysis was allowed to go on several weeks, the pressor effect came on more quickly, was greater in degree and shorter in duration. They observed that while organic solvents did not remove the pressor agent from fresh press-juice, such solvents did extract a highly potent pressor principle when used on autolyzed press-juice. From the older autolysates a pressor principle was readily obtained by ultrafiltration while the ultrafiltrate of fresh press-juice was inactive. They explained their findings by assuming that "renin" was bound in combination with a protein and that this combination was broken up by autolysis. They concluded that the pressor agent obtained from their autolysates was a small molecular basic substance, probably an amine. Recently Hessel and Maier-Hüser[14] claim to have prepared "renin" in a highly purified form and administration of minute doses (0.2 mg.) to dogs caused a pronounced and sustained rise in blood pressure. No information was given concerning the method of purification.

The experiments to be described were carried out for the purpose of learning more concerning the nature of the renal pressor substance in the hope that by this means it might be possible to make assays of the pressor content of hypertensive kidneys uncomplicated by the confusing effects of coëxisting depressor agents.

Methods. With dogs as test subjects, it was found that anesthesia had a pronounced influence on the results. Extracts which were pressor in unanesthetized dogs sometimes produced only a decline in blood pressure when injected into anesthetized animals. (This was later found to be due to increased sensitivity of the anesthetized animals to depressor bodies also in the extracts rather than to a reversal of the effect of the pressor agent.) Hence, all the experiments described were carried out on unanesthetized dogs especially trained for these experiments. Most of the blood-pressure measurements were made by means of a cuff similar to that described by Ferris and Hynes,[5] applied to the hind leg, the passage of the pulse wave being determined by palpation of the dorsal artery of the foot.

When an extract was to be tested, the dog with the blood-pressure cuff in place was allowed to rest on his side on the table for several minutes. Seven measurements of blood pressure were than made, the highest and lowest readings discarded and the average of the other 5 measurements considered as the control value. When any considerable variation in these readings was encountered a second set of control readings was taken, usually by a different observer. After it was apparent that the dog's blood pressure was constant the material to be tested was administered into a superficial vein of one of the legs. Following the injection the blood pressure was measured at intervals of ½ to 1 minute. The rise in blood pressure was considered to be the difference between the average of the 3 highest successive readings after the injection and the average control value.

A few observations were made with a cannula in the femoral artery, using local novocaine anesthesia.

It was found that some unanesthetized dogs, while remaining perfectly quiet, exhibited well-marked spontaneous changes in blood pressure. Furthermore, it was observed that different dogs displayed marked variation in the response of the blood pressure to injections of the same preparation. Because of these variables mentioned it was not possible to obtain constant effects. With each of the various preparations used, occasionally depressor responses, or no response at all, were obtained and test fractions which ordinarily were inactive, or depressor, occasionally were pressor. Such variations were inherent in incompletely purified preparations, especially when one is using unanesthetized animals, and it is not believed that the occasional atypical responses can be considered as seriously impairing the conclusions to be drawn. In reporting the results we have depended on the effects obtained in the great majority of instances from a given preparation.

Fresh pig kidneys were obtained from the slaughter house. Cortex and medulla were quickly separated, the cortex passed through a meat grinder, and ground in a mortar with carborundum and 2 cc. of physiologic saline per gram of cortical tissue. After 10 to 20 minutes' grinding the mixture was centrifuged and the supernatant suspension separated and employed for injection or for various extraction procedures described below. The amount of the final extract injected usually corresponded to 10 or 20 cc. of saline extract, *i. e.*, 5 or 10 gm. of the original kidney cortex.

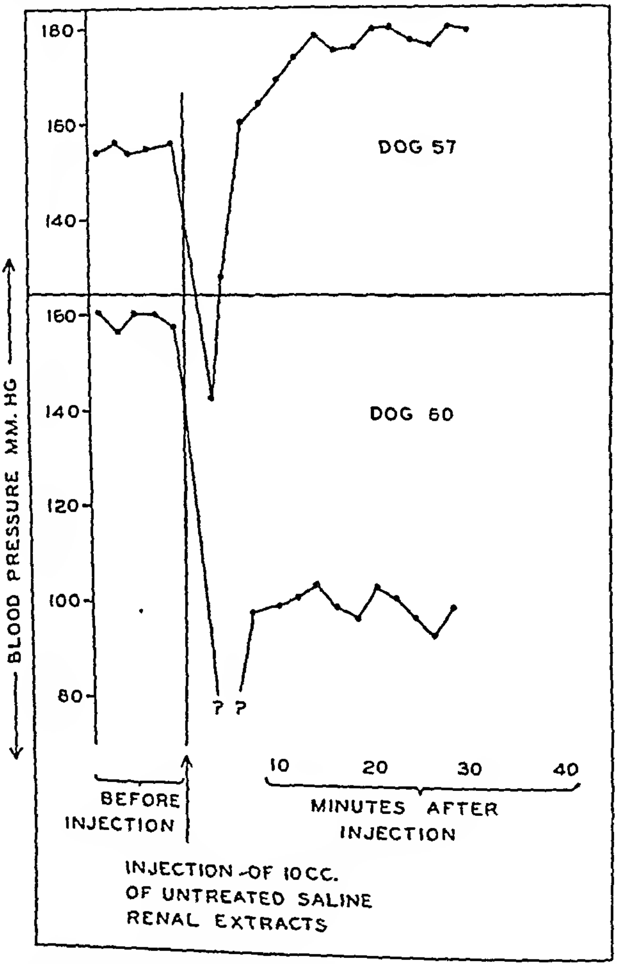

FIG. 1.—The upper part of the figure illustrates a typical result—a temporary fall in blood pressure being followed by a sustained increase. The lower part illustrates an experiment in which only the depressor effect was observed.

Results.—*Saline Extract.* Several score experiments were performed with varying results. In most of the experiments a pronounced and occasionally fatal fall in blood pressure occurred immediately after the injection. Often the blood pressure remained low for several minutes, gradually returning to the normal level. Frequently the preliminary decline in blood pressure was followed by a prolonged and sustained elevation and in some instances a rise occurred without the preliminary decline. The maximum increase was not usually observed for several minutes and it was usually sustained for 20 minutes or longer before gradually returning toward the control level. Some dogs reacted regularly with a depressor effect, others with a diphasic result and still others showed only the pressor response. More commonly a given dog displayed varying responses. Illustrative experiments are shown in Figure 1.

Fractions Obtained by Precipitation With Ammonium Sulphate. Bengel and Strauss[1] found that the active pressor substance was not precipitated by 1/3 saturation of ammonium sulphate but did come down with 7/12 saturation of this salt. Consequently, preparations were made as follows: Ammonium sulphate was added to 1/3 saturation to the fresh saline extract. After standing overnight the suspension was centrifuged, the supernatant fluid made up to 7/12 saturation and again allowed to stand overnight. The two precipitates—that coming down with 1/3 saturation and that brought down between 1/3 and 7/12 saturation—were then suspended in water and both of them as well as the supernatant fluid from the 7/12 saturation were dialyzed for 12 to 15 hours against flowing

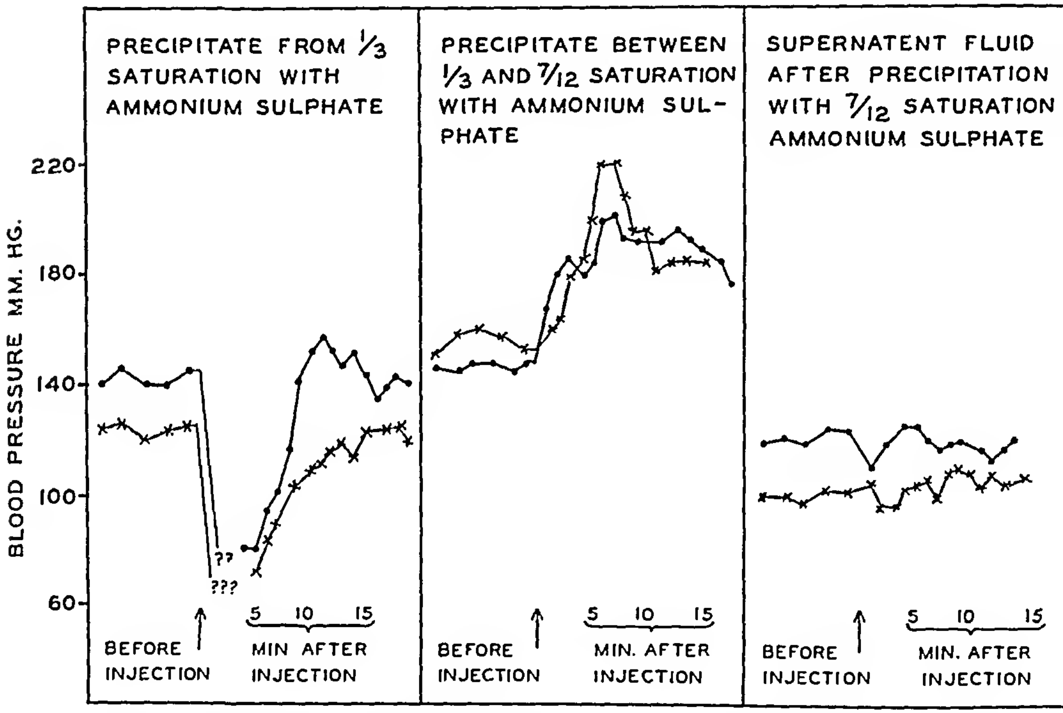

FIG. 2.—The chart shows the effect of various fractions of renal extract after treatment with ammonium sulphate. The precipitate from 1/3 saturation was usually depressor; the fraction precipitated between 1/3 and 7/12 saturation was usually pressor; the fraction remaining in solution after 7/12 saturation was inactive.

tap water.* The three fractions were then tested for their pressor properties. Although some variation occurred in different experiments the general trend of the results, which is illustrated in Figure 2, was quite clear. The precipitate at 1/3 saturation usually gave only depressor effects, that between 1/3 and 7/12 saturation was ordinarily pressor, and the final supernatant fluid was inactive. These results, in agreement with those obtained by Bengel and Strauss[1] and by Hartwich and Hessel,[12] indicate that the active principle has the properties of a protein.

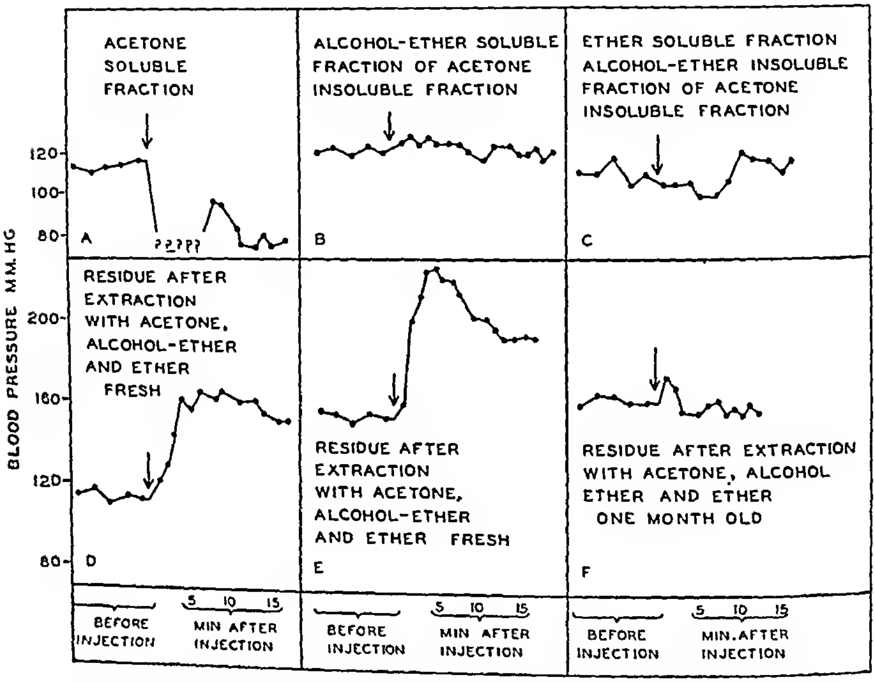

FIG. 3.—Fresh renal extract was successively treated with acetone, alcohol-ether mixture, and ether. The acetone-soluble fraction was usually depressor (*A*). The alcohol-ether and ether-soluble fractions were inactive (*B* and *C*). When the residue left after extraction with these organic solvents was taken up in physiologic saline solution a pressor effect was obtained (*D* and *E*). This pressor agent was unstable (*F*).

Fractions Obtained by Precipitating With Acetone. Five volumes of acetone were added to 1 volume of the fresh saline extract, the mixture was shaken for 5 minutes, allowed to stand for an hour and centrifuged. The precipitate was shaken with alcohol-ether solution (3 parts alcohol to 1 part ether) equal to the volume of the original saline extract. After centrifuging, the precipitate was shaken with ether and again centrifuged. The final precipitate was dried and pulverized in air and immediately shaken with 0.9%

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* Non-protein nitrogen determination on these dialyzed preparations showed them to be practically free of ammonium sulphate.

sodium chloride and centrifuged, the supernatant fluid being employed for injection.

Typical results obtained by the injection of these several fractions are shown in Figure 3. The acetone-soluble fraction (after removal of the acetone *in vacuo*) was either inactive or, more commonly, depressor. The alcohol-ether and ether-soluble fractions (after removal of these solvents) were inactive. The saline extract of the final residue after extraction with the above solvents usually gave a slowly developing, sustained and fairly pronounced pressor effect (Fig. 3, *d* and *e*). The blood pressure raising principle obtained by this method was quite unstable (Fig. 3, *f*), and on standing at room temperature rapidly became inactive. It was also noted that when the original saline extract was several days old the final preparation

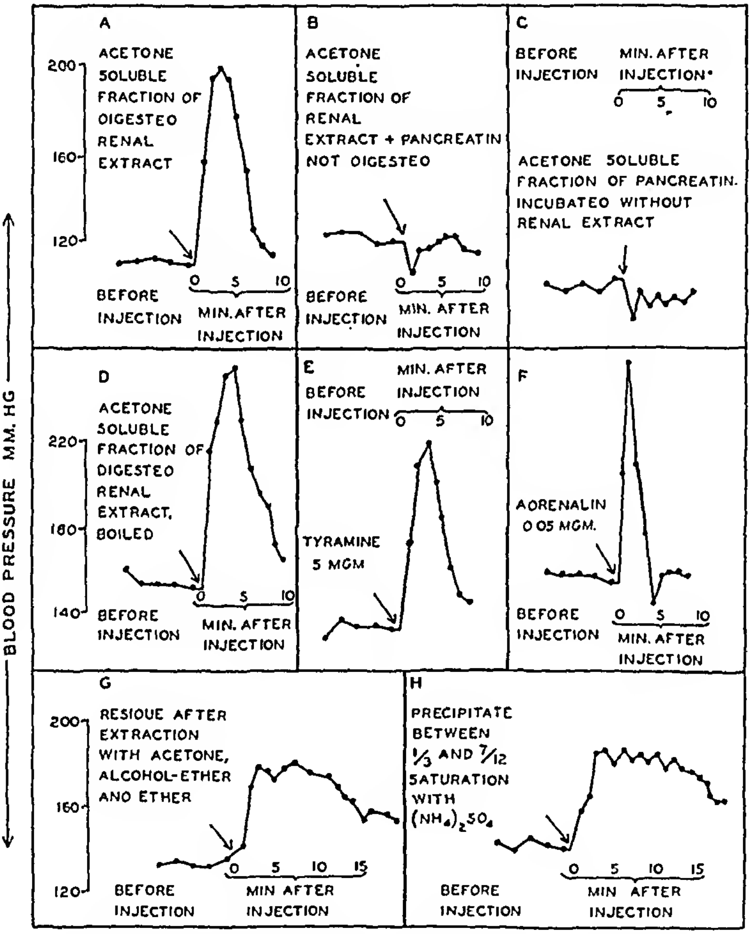


Fig. 4.—After digestion of renal extract with pancreatin, an acetone-soluble, powerful pressor agent was obtained (*A*). Material similarly treated but not digested gave no such effect (*B*). Incubation of pancreatin solution alone yielded negative results (*C*). The active pressor agent was heat-stable (*D*) and its effect was identical with that of tyramine (*E*), being more lasting than that of adrenalin (*F*) and more evanescent than that of the pressor substances obtained by precipitation with acetone (*G*) or with ammonium sulphate (*H*).

usually had a pronounced depressor action, or would be totally inactive.

Whether the active principle obtained by this method is identical with that obtained by ammonium sulphate precipitation is uncertain. Their effects on blood pressure were similar; however, the pressor agent obtained by precipitation with acetone was much less stable than that secured by treatment with ammonium sulphate.

Fractions Obtained by Digestion. It was found by Hessel and Hartwich, as mentioned above, that when renal press-juice was allowed to autolyze for several weeks at 37° C., the pressor substance was ultrafiltrable. In an attempt to reproduce these results more quickly we have studied the effects of digested renal saline extract. Freshly prepared extract was adjusted with phosphate buffer and sodium bicarbonate to approximately pH 8. Pancreatin was added and the mixture incubated at 37° C. for 12 to 16 hours. The digest was found to be powerfully depressor; however, when it was extracted with acetone the acetone-soluble fraction proved, after removal of the remaining depressor agents by extraction with petroleum-ether and removal of the solvents, to contain a pressor substance. This pressor effect was not obtained when pancreatin solution without renal extract was incubated, or when acetone was added to an unincubated mixture of renal extract and pancreatin, and appeared to be formed by the process of digestion (Fig. 4, *a*, *b* and *c*). It was found that the potency of this material was not diminished by boiling (Fig. 4, *d*), that its effect came on more rapidly, was more pronounced and disappeared more quickly than did the effects produced by the injection of the protein-like pressor substance produced by the previous precipitation methods (Fig. 4, *a*, *d*, *g* and *h*). The pressor response was less immediate and of longer duration than that produced by adrenalin (Fig. 4, *a* and *f*); on the other hand, the response of the blood pressure was identical in character to that produced by the injection of tyramine (Fig. 4, *a* and *e*). In each case the pressor response reached its peak in 2 to 4 minutes and lasted 6 to 8 minutes.

As illustrated in Figure 5, added tyramine could be quantitatively recovered by the procedure used in isolating the pressor substance from the digested mixtures. It has been shown by Tainter and Chang[20] that the pressor effect of tyramine can be abolished by the previous administration of cocaine. This effect is not specific for tyramine.[3] The pressor substance obtained from the digested renal extract was found to be reversed by a preliminary injection of cocaine (Fig. 6, *d*), whereas the pressor response of the other fractions described above was unaltered. Since there is no reason to suspect the presence in tissue digests of pressor agents—other than tyramine-like substances—which are inhibited by cocaine, these observations suggest that the pressor agent in the digested renal extract is a substance with properties similar to those of tyramine, that it is

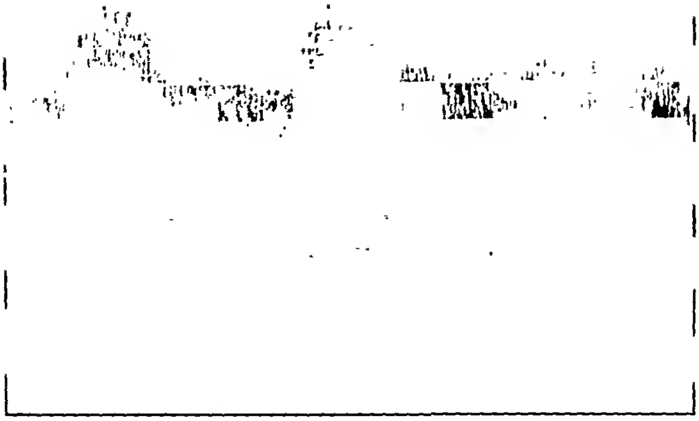
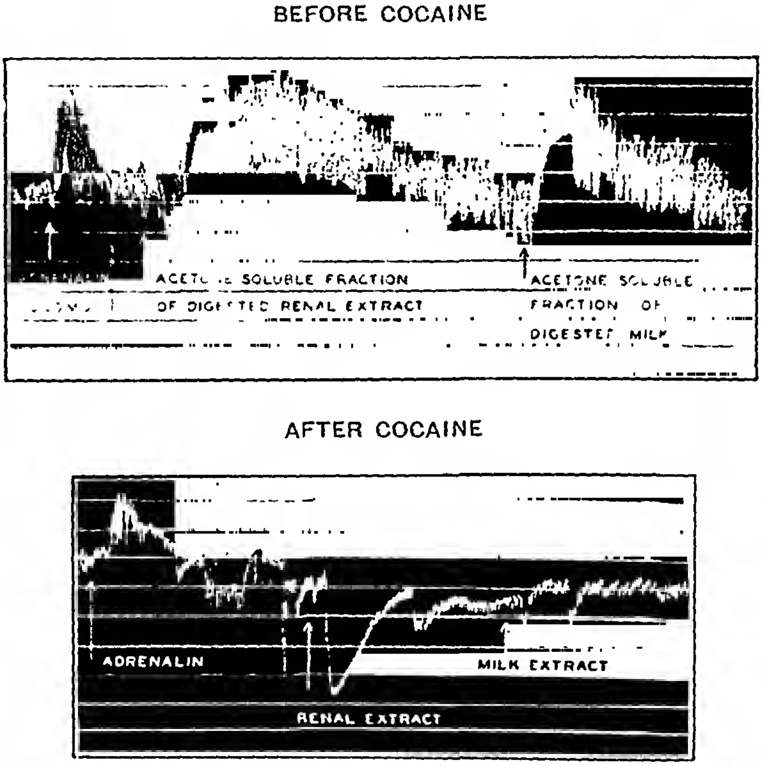


FIG. 5.—A solution of tyramine comprising 3 mg. of tyramine per cc. was treated similarly to digested renal extract, *i. e.*, with acetone and with petroleum-ether. The figure shows that the tyramine was recovered quantitatively from the acetone fraction; the petroleum-ether fraction having a negligible pressor effect. (The distance between two adjacent horizontal lines indicates 20 mm. of mercury.)



BEFORE COCAINE

AFTER COCAINE

FIG. 7.—The figure shows that the pressor effects obtained from digested milk and from digested renal extract were abolished by cocaine; that of adrenalin was not. (The distance between two adjacent horizontal lines indicates 20 mm. of mercury.)

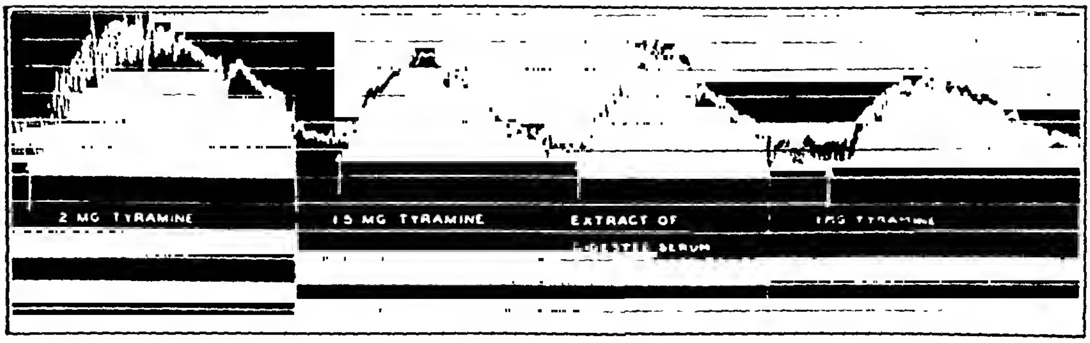


FIG. 8.—The injection of extract of digested pig serum (the amount indicated corresponding to 5 cc. of serum) gave as great a pressor effect as did 1.5 mg. per kg. of body weight of tyramine. (The distance between two adjacent horizontal lines indicates 20 mm.

produced in the process of digestion, and that it is not responsible for the pressor effect of the fresh renal extract.[*] The blood pressure raising principle in the latter appears to be dependent on an entirely different substance of a protein-like nature, which exists preformed in the extract, is precipitable by the methods described, and appears to correspond with Tigerstedt's "renin;" the former substance seems to be the pressor agent which develops after several hours' digestion of renal extract, and is probably the pressor principle occurring in such extract after prolonged autolysis. A series of observations were made on extracts which had been rendered sterile by filtration or by the addition of disinfectants. The results obtained were inconclusive and we are not entirely certain whether the pressor substance can be produced by digestion in the absence of bacterial growth.

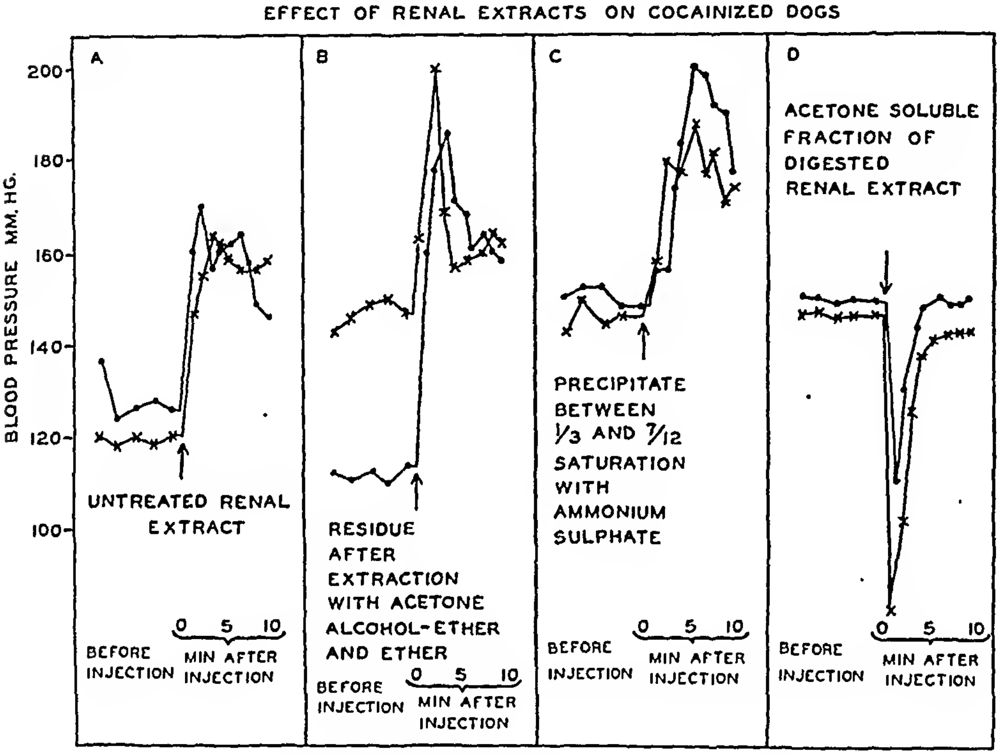


Fig. 6.—The previous administration of cocaine did not prevent the pressor effect of fresh renal extract, of renal extract precipitated by organic solvents or of renal extract precipitated by ammonium sulphate. However, cocaine did prevent the rise in blood pressure produced by the acetone-soluble fraction of the digested renal extract.

Extracts of Other Tissues. In order to determine whether the pressor principles obtained by these various methods were specific for renal tissue, similar preparations were made from other organs (Table 1). It is seen that precipitation with acetone or with

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[*] Further efforts to identify this substance as tyramine by the Gerngross reaction, and preparation of tyramine di-benzoate were not attempted.

TABLE 1.—EFFECT ON BLOOD PRESSURE OF ORGAN EXTRACTS.

Method of extraction.		Organ from which extract was prepared. Liver.	Spleen.	Lung.	Heart.
Precipitation with acetone, alcohol-ether and ether	Number of tests	3	4	3	4
	Number of times blood pressure increased*	0	0	0	0
Precipitation with ammonium sulphate	Number of tests	4	4	6	0
	Number of times blood pressure increased*	0	0	0	0
Digestion and extraction	Number of tests	5	3	3	2
	Number of times blood pressure increased*	4	3	2	0

* Increases of less than 20 mm. of mercury were considered as negligible in compiling this table.

ammonium sulphate of the saline extracts of liver, spleen, lung and heart did not yield a pressor substance. However, when saline extracts of liver, spleen and lung were digested, an acetone-soluble powerful pressor agent was obtained which was similar in all respects to that obtained from the kidneys. Application of the same technique to milk and white beans gave positive results in each of 3 instances. On the other hand, negative results were obtained from heart (2 tests), Jack beans (3 tests), sweet potato (2 tests), gelatin (2 tests), egg white (2 tests) and corn meal (1 test). The pressor effect obtained from substances which gave positive tests was also inhibited by cocaine (Fig. 7).

In a number of instances pig serum was digested with pancreatin and also yielded a powerful pressor substance similar to that obtained from digested renal extract (Fig. 8). This pressor effect was not obtained from unincubated serum with or without pancreatin, and was not secured from serum incubated without pancreatin (Fig. 9).

Discussion. The foregoing observations indicate that there can be obtained from renal extracts, 2 different pressor substances. One of these appears to be a protein, having some of the properties of pseudoglobulins. Its action comes on slowly after intravenous injection, the pressor response to it develops slowly and is quite prolonged. This substance corresponds to that designated as "renin" by Tigerstedt and Bergman.[22] The other pressor agent is not present in fresh renal extract but can be produced by digestion. It has chemical, physiologic and pharmacologic properties which insofar as they have been tested are similar to those of tyramine. This latter substance is not specific for kidney tissue, but can be obtained from digested extracts of various organs and of certain vegetables. It can also be obtained from digested serum.

One is naturally interested in knowing whether the 2 compounds under discussion are of any significance in hypertensive states. On this question the experiments reported in the present paper throw no direct light. However, Harrison, Blalock and Mason[9] and

Friedman and Prinzmetal[6] showed that fresh saline extract of kidneys rendered ischemic by the application of a Goldblatt clamp to the renal artery usually had a more pronounced pressor effect than did similar extracts of the opposite normal kidney of the same dog. These findings suggest that "renin," which appears to be responsible for the pressor property of untreated renal saline extracts may be of some importance in the production of the increase in blood pressure displayed by the animals with renal ischemia produced by applying a Goldblatt clamp.

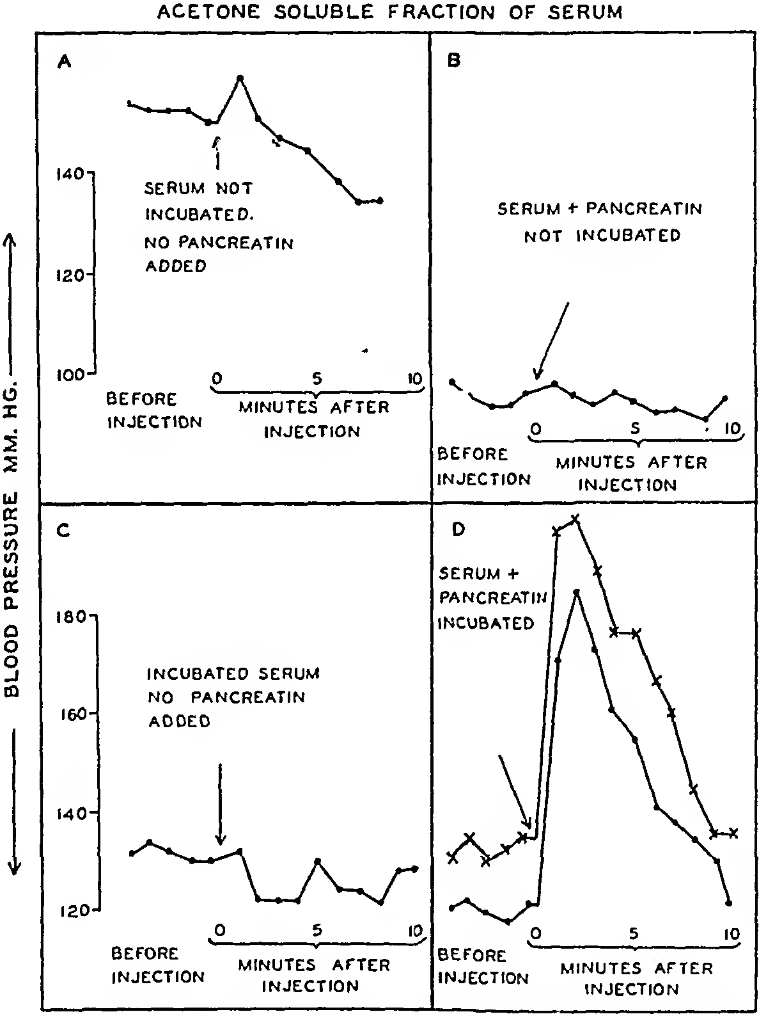

Fig. 9.—Acetone extracts of fresh serum (*A*), fresh serum plus pancreatin (*B*), and of serum incubated without pancreatin (*C*), were not pressor. However, incubation of a serum to which pancreatin had been added yielded a potent pressor substance (*D*).

Whether tyramine or tyramine-like substances are of any significance in the production of hypertension is uncertain. Some authors believe this to be the case;[17,23] others hold the reverse view.[13] Our own experiments only emphasize again the readiness with which they form under condition of protein degradation. The condition of the method of preparation which we have used, *i. e.*, pancreatic digestion plus bacterial action, could exist only in the intestinal tract. It would seem that observations concerning the formation of pressor substances in the gastro-intestinal canal and concerning the ability of the liver or other organs to remove them from the portal blood in states associated with hypertension might be useful. The possibility of the formation of tyramine in other sites in the body should also be investigated.*

Summary. 1. A pressor principle can be separated from fresh saline extracts of renal cortical tissue by ammonium sulphate precipitation. The properties of this substance are those of Tigerstedt's "renin," and it appears to be responsible for the pressor effects of fresh untreated saline extract of kidneys.

2. A pressor principle can be extracted from the acetone-insoluble fraction of renal extract by appropriate treatment. This principle has certain properties resembling those of "renin," but it is not known whether the two are identical.

3. Autolysis or digestion of renal extract results in the appearance of a pressor principle which has some properties of tyramine.

4. Evidence is submitted that the pressor effects of fresh saline extract of kidney is not due to tyramine, or a tyramine-like substance.

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* Since this paper was prepared for publication further investigations have yielded two additional points of importance 1, The rat, anesthetized with sodium pentobarbital, is a more satisfactory test object for these extracts than is the unanesthetized dog 2 for use in the rat the most satisfactory method of preparation of the renal pressor substance corresponding to "renin" is precipitation with alcohol, and reextraction of the pressor body from this precipitate with water. The details of these experiments will be submitted in a later publication.

MARIHUANA.

OUR NEW ADDICTION.*

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WITH lurid and startling headlines, the public press has announced: "Spread of Marihuana Held Menace to Country's Youth." "The Fight Against Hashish of America." "Reefer Peddler Held in $15,000.00 Bail." "Marihuana Spreads Its Net in America." "America Menaced by New Dope Evil." "Marihuana —Assassin of Youth." "Sex Crime Epidemic Laid to New Dope."

Marihuana, spelled different ways, is not the proper name of the drug, its addiction is not new, except with us, nor are the effects of indulgence so baneful as the foregoing headlines would indicate. Nevertheless, during the last 10 years, its excessive use had become sufficiently prevalent to cause all states except North Carolina and Tennessee, to enact legislation against its distribution. Finally, the Federal government regarded the situation so serious that control of the growth of the plant was sought through the imposition of certain excise taxes, which resulted in the enactment of a bill at the last session of congress, giving marihuana a separate listing among narcotic drugs, a law that actually became effective October 1st of this year. The distribution of this plant is so widespread that, in addition to its cultivation, it may be found growing wild along the roadsides and upon vacant lots in many states, particularly in the west. Even Philadelphia County has not escaped. In San Quentin, California, and in the Colorado State Reformatory, it was found growing within the prison walls, where it was being harvested and smoked by some of the inmates. Since a number of marihuana's products have important legitimate, commercial uses, enforcement of this law may be attended by some of the difficulties encountered during our Prohibition era. With us, the proper name of the plant is cannabis sativa; cannabis, cannabis indica, Indian hemp and hashish are synonymous terms. Marihuana is a mongrel, Mexican word, meaning pleasant feeling. In underworld argot, the drug is known by many different names, such as, "Indian hay," "greefo," "mu," "Inotta," "mooter," "reefer," and "Mary Warner" is marihuana personified.

Historical Survey. We are repeatedly told that from the Arabic, "Hashishan" (herb-eaters), comes our word, assassin, though this is questioned by the biographers[5] of Omar, that tent-maker of old. In Persia, long before the Christian era, there lived a military and religious sect known as the Assassins, who were sometimes incited to greater violence in their atrocities, by the use of hashish, which is the historic name of marihuana. The plant had its origin in the

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* Read before the Philadelphia Neurological Society, November 19, 1937.

East and preparations made therefrom were either smoked, chewed or drunk. Homer told of the power of hashish to afford solace in our moods of distress, as well as of its more harmful effects. The growth was cultivated in China three centuries before Christ; writings of the Assyrians, Greeks and Romans, all speak of familiarity with its use, and in Sanscrit was recorded the popularity of "Gaiety Pills," made from hemp and sugar. About 1800, when Napoleon's army was in Egypt, he found it necessary to prohibit its use by his soldiers. In addition to smoking hemp, the natives of India prepare from the powdered leaves a beverage called "bhang," and a similar drink of the Greeks was "nepenthe." In Egypt, now as in ancient times, it has many devotees; elsewhere in northern Africa, the habit is a powerful one, hashish often being preferred to alcohol or opium. At times, the drug has played an important part in religious observances. From India, it spread to Mongolia. Both hashish and opium are charged with having caused the Malayan to run "amok," but those murderous episodes often occurred without such drug domination. In time it appears the plant was introduced from the eastern hemisphere to Mexico and from there spread to the United States. Our early settlers, finding its fiber useful, began its cultivation.

The Plant and Its Use. This hardy, annual growth thrives in most climates with little cultivation. The plant is slender with an erect, thick, stringly, angular and branching stem, varying in height from 3 to 16 feet; the leaves which grow alternately and for the most part point downward, are formed of from 5 to 7 blades with saw-toothed edges. Considerable commercial value attaches to the plant. From its fiber, twine, rope, bags and clothing may be made. When ripe, the small, whitish flowers at the top of the female plant are found to yield a sticky, greenish, resinous substance which contains the active principle of marihuana; however, recent research by Munch, showed definitely that the substance may also be obtained from the male plant. Botanists tell us that scientifically, the seed is a fruit. From this seed, a rapidly drying oil may be extracted, useful as an ingredient of paints and varnishes; the oil also finds use in the manufacture of soap and linoleum. The seed is an important food for pigeons, acting as a general tonic and unexcelled in maintaining a healthy condition of their plumage; doubtless seed spilled from their feed boxes is responsible for some of the patches of marihuana found growing wild. It is said application of heat and moisture soon destroy all power of germination, so that an easy method of sterilization appears to be available. In the Orient, when food becomes scarce, the seed is ground and eaten as we eat oatmeal. Therapeutically, marihuana's preparations have been used for the relief of pain, in migraine, to produce a euphoria and to overcome nervousness; but the drug has mostly fallen into disuse, partly owing to its greatly varying degrees of potency. John Stuart Mill, philosopher, wrote of its power to revive forgotten memories, and in my inquiries, smokers have frequently informed me that while under its influence, they are able to recall things long forgotten. If through such use, the unconscious mind could be rendered more accessible, possibilities as an aid in psychoanalysis and psychotherapy are shown.

Effects of Excessive Use. The active principle of the plant, cannabinol, chiefly affects the cerebrum and excessive use results in what is known as cannabinism. While portions of the plant may be chewed or beverages made therefrom, with us, indulgence for the most part is through cigarettes, known in slang as "reefers;" a reefer is made of brownish paper, shorter and thicker than the common cigarette; and in price ranges from 10 cents each to 2 for 25 or 35 cents. The smoke which is always inhaled, is retained much longer than is the custom in cigarette smoking. The odor given off is said to be rather distinctive. Though varying greatly in strength, 2 or 3 reefers usually have the desired effect. The product may also be purchased in bulk—a mixture of most parts of the plant. Extent of effect depends upon potency of the plant, care in curing the product, individual susceptibility and the quantity used. Often, the first noticeable change is a lessening of the subject's power fully to control his thoughts and actions. Distractibility is shown by rapid interruptions in the continuity of thought and by the many disconnected ideas that thrust themselves into the field of consciousness. In addition to a feeling of exhaltation and euphoria, the smoker is aware of increased power and energy. By a determined effort of the will, he is for a time able to withdraw from his reveries, but if there be further indulgence, such possible lucid intervals become shorter and less frequent. Illusions are common and faces of others often take on grotesque expressions. Imagination may be stimulated to the extent of delirium, sometimes with fascinating hallucinatory creations appearing; these may be pleasing, ludicrous, gruesome or sensual. Inhibition being much reduced, dominant emotions become magnified and thus, as is often observed, no two persons are similarly affected; the genial man grows more fond of his fellows, the quarrelsome one pugnacious, the timid one more fearful and the criminal is emboldened. Exaggeration is the rule, so that the plainest food may taste delicious and hearing may be painfully intensified. Perception is disturbed in the matter of time and space; minutes seem hours and hours days; to pass over a twig a long step or a jump may be taken. Excitomotor activity is often present and a reckless abandon that may extend to violence. Sensations of pain and touch are diminished and the pulse rate is increased. With the full return of consciousness, no subsequent ill effects are experienced. Marihuana is a diuretic and its use induces hunger. Since the craving that accompanies alcohol and morphine addiction are not present, indulgence can be easily discontinued. There are no known fatalities. Marihuana is said to be a source of inspiration for some writers, painters and other artists. Of one whose confidences he received oftener than he desired, Ribot[4] said: "I once knew a man who for 20 years constantly took hashish in large doses; he withstood the drug better than might be expected, but finally died insane." The French poet, Baudelaire,[6] a member of the Hashish Club in Paris, used hashish and wrote about it; he also used alcohol and opium, and had a coarse, insatiable, colored mistress; he contracted syphilis before 20 years and died at 46, according to Lombroso, of paresis; but from the description, it appeared more like another form of syphilis; however, it seems unlikely that hashish was more than contributory to his end.

Lewin,[2] the Berlin authority on narcotics, divides eaters and smokers into three groups: 1. Exhibit a state of general euphoria and excitement with hallucinations and illusions even extending to deliria, less aggressive, however, than that of alcohol. They may be irresponsible for the time being. A cure may usually be effected in a day. 2. An acute mania develops. The patient is agitated, garrulous, suffers from insomnia, there are sense illusions, delusions of persecution and sometimes a violent fury. The condition may last months and is not always curable. 3. A group of mentally weakened individuals who pass into a maniacal state after every excess of hashish; they are overtalkative, lazy, but the slightest provocation may evoke a violent state. After dismissal from the hospital they relapse, become agitated, insult their friends and easily show violence. Many such chronic subjects are incurable and end in dementia. Individuals of this group seldom commit crimes. Generally speaking, it is said the sudden and rapid cure of such diseases, is the only diagnostic sign of insanity due to hemp. In Bengal, of 232 cases of mental disease, 76 were caused by hemp, only 34 of which were cured. In Cairo, out of 248 inmates, 60 men and 4 or 5 women owed their mental disease to hashish. But these statistics are from lands where indulgence is very extensive and has been carried on for generations. Lewin believes it probable that the craving for hemp may be inherited. As to its being an aphrodisiac, he states: "Perhaps sexual potency is increased at the outset, but it nevertheless diminishes during the subsequent addiction of the drug, as is the case of opium smoking."

Those of us who were students of H. C. Wood, the elder,[8] will recall the vivid description by him of his personal experience after taking a large dose of cannabis indica extract. The first manifestation was noticed several hours after, while in the house of a patient during the writing of a prescription; he seemed entirely oblivious of his surroundings; then, catching himself, he apologized for what to him seemed a tremendously long time, but the patient assured him he had only been a few minutes. Returning home, he found himself somewhat excited and with an inward feeling of joyousness. Physical fatigue was banished and idea after idea raced through his mind. Self-control was lost, he laughed and made funny gestures. His legs felt numb, his mouth dry, the pulse was 120, and becoming alarmed, he summoned a fellow practitioner; seeing the physician approaching, Wood observed that he seemed a vast distance away and a corresponding time coming toward him. His legs felt heavy and pinching them caused no pain. There were periods when he seemed unconscious though it was possible for him to be aroused. A disturbing feeling of personal antagonism between himself and his will power was experienced. Double consciousness was present—a feeling that he was himself and someone else at the same time. There were no hallucinations and no aphrodisiac reactions. Urinary secretion was markedly increased. About 8 hours after ingestion, he went to bed and wakened in the morning with a clear mind, though soon after, and from time to time during the day, there were brief fragmentary experiences similar to those of the night before. Except for a marked anesthesia of the skin all day, there were no unpleasant after effects.

In the Eastern State Penitentiary we have many colored prisoners, some of whom had been thoroughly familiar with reefer smoking as well as with the atmosphere where provision was made for such indulgence. However, in none of these prisoners had there been any evidence that marihuana was a factor in their crimes. One prisoner who had been a periodic smoker for 17 years, was an adept at curing the product which he stated was similar to that used for tobacco. Another who was particularly informative, had been proprietor of a "club," "den," or "tea-pad," slang for places where reefer smokers congregate. It is said such clubs exist in most large cities. One of the more expensive of these was described as a room sufficiently large to accommodate two dozen devotees, with smaller adjoining rooms for their more intimate relations. The smokers were usually dressed in silk pajamas and would sit or recline upon the many silken pillows disposed about the floor; upon the walls were hung pictures and other objects, mostly of women, chosen for their sensuous or sensual appeal. Such rooms were purposely unventilated, and an initiate, entering the heavily charged atmosphere, would soon come under the influence of marihuana. The lights are low, which is more conducive to reveries and perhaps to mating. Music is softly played, though by way of diversion, coming from a phonograph, may be heard the sonorous and sensual voice of Cab Calloway, singing "That Funny Reefer Man." It is said the acts of many such entertainers is preceded by the smoking of reefers. Various slang terms are used by addicts, the more common ones being, "in," meaning the subject is under the influence, and "out" which is the reverse; "high," is the state desired to attain and to maintain for some time; this "high" effect is present when some object that is being observed, grows smaller and smaller, until only a blurred spot remains. The experienced smoker is able to go "in" and "out" at will. Reactions vary with different individuals; they may talk, many laugh, sing, dance or sleep; most of them are happy, some are quarrelsome and upon little or no provocation become assaultive; many prefer to sit or recline alone, given over to their reveries; most objects seen are reduced in size and time is greatly lengthened. A few, becoming grandiose, have but to desire something, when seemingly, it is realized—wish-fulfillment not Freudian in origin. The ability to recall in detail things long forgotten, was frequently told me. Any sudden shock has a sobering effect; or, if it is desired to come rapidly out of the "drunk," taking copious quantities of cold water, or a cold bath, together with an abundance of fresh air, will soon restore the addict. These colored subjects insist that marihuana is an infallible remedy for toothache.

Relation to Crime. Homicides, suicides and assaults, particularly those upon sex, are among the more grave indictments of marihuana. Perhaps the most lurid and frequently repeated case is that of a Florida youth, who, while said to have been under the influence, imagined some people were going to cut off his arms and legs; whereupon, in a frenzy, he seized an ax, killed his father and mother, 2 brothers and a sister. One man, greatly to his horror when coming from under the influence, learned that he had decapitated his best friend. Still another, becoming enraged at his wife, killed her in the street before many witnesses. A high-school girl had heard some whisperings concerning the "kick" offered by the new kind of cigarette; after smoking a reefer, she was able to dance long without fatigue; time became elastic and in her state of exhilaration all else seemed inconsequential; studies were entirely neglected, she became despondent, but a few puffs on her faithful cigarette brought relief; finally, coming to full realization of her school problem, she deliberately walked to an open window and leaped to her death. Thus, says the report, did marihuana solve her problem. These cases and similar ones have been very incompletely reported, since we do not know what other factors may have entered into their acts of violence.

By way of contrast, the following references are given: In 1932, this announcement was made by the State Narcotic Committee of California: "The sensational statement that peddlers are selling narcotic drugs to minors cannot be substantiated by our records." From the archives of the International Narcotic Education Association, there were reported 8382 problem children, from 28 typical American communities; of these, 29 were reported as drug addicts, but 26 were only using snuff, one little girl had used headache powders, a boy had purchased a drugged cigar, and a third case was of unknown nature. At the Bellevue Hospital, Bromberg[1] found in 361 subjects classed as psychopathic personalities, 32 were drug addicts, only 7 of whom had smoked marihuana for any considerable time, and none of the assault cases investigated, "could be said to have been committed under the drug's influence." As observed in his experience, "the anti-social, aggressive and sadistic elements of the personality uncovered by the drug are responsible for the crime rather than any specific crime-producing properties of marihuana." Bromberg further adds: "It is probable that alcohol is more responsible as an agent in crime than marihuana."

Perhaps the most extensive use of the drug is found in New Orleans where, in 1934, it was said one out of every four persons arrested was a victim of the drug. Eugene Stanley,[7] district attorney of New Orleans, in speaking of the difficulties experienced in determining the degree of responsibility in one under the influence of marihuana says: ". . . while some of these experts are conversant with the nature and effect of the drug, it has been the experience of the author that many psychiatrists know nothing whatsoever of the effect. . . ."

Summary. Known in history as "hashish," and in a recent congressional act as "marihuana," *cannabis sativa* grows so widespread in this country and has such important commercial uses that law enforcement may be hampered. From marihuana's fiber, twine, rope and bags are made; it yields a rapidly drying oil, useful as an ingredient of paints and varnishes and in the manufacture of soaps and linoleum. Birds thrive on the seed.

Therapeutically, marihuana has been employed for the relief of pain, in migraine, to overcome nervousness and to produce euphoria; but the drug is now seldom used, owing to its greatly varying degrees of potency. Its use causes things long forgotten to be recalled in detail, an effect that invites careful research. Preparations of the plant are smoked, chewed or drunk, but in this country indulgence is mostly through cigarettes, known in slang as "reefers."

Marihuana is not a habit former like opium and cocaine; from a so-called "drunk," there are no hangover symptoms and there are no known fatalities.

But even moderate use is not without danger—its well known action on perception, the lengthening of time and space, could prove most disastrous if, for instance, the smoker were driving a car. When used daily in large quantities, the direct action upon the cerebrum often causes chronic mental deterioration, an effect that has been known for ages in India and Egypt.

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THE STERILITY OF ALCOHOL.

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Forty years ago, Minervini[15] and later other workers demonstrated that non-spore-forming organisms could be killed by alcohol. Diluted alcohol was found to be more effective than alcohol of high concentrations, that of 70% strength being the most efficient. Minervini using the thread method noted that while a 70% alcohol killed the *Escherichia* (Bacillus) *coli* and *Staphylococcus aureus* in 60 minutes, dehydrated or absolute alcohol required at least 12 hours for the former and more than 3 days for the latter organism before destruction was complete. Olitsky and associates[18] and others, however, have reported that the addition of alcohol to body fluids results in the production of dense coagula which protect microorganisms and prevent penetration by the alcohol.

The inefficiency of alcohol as a germicidal agent for spore-forming bacteria has been demonstrated repeatedly. In 1881, Koch[11] showed that neither dilute or strong alcohol would kill anthrax spores in 110 days. Minervini[15] and Russ[20] confirmed Koch's work. Stokvis[24] revealed that *B. megatherium* remained viable for 2 weeks in alcohol. Heim[9] was able to cultivate *anthrax bacilli* from infected threads which had been immersed in alcohol for 20 years. Dozier[6] found that alcohol possessed no bactericidal effect upon the spores of *Clostridium botulinum*. Nye and Mallory[17] reported the inefficiency of alcohol upon the spores of *Clostridium welchii* in a routine procedure of disinfecting surgical instruments, such technique having resulted in a serious outbreak of infections following operations. Schmidt,[23] in an investigation of catgut, reported that the sterile catgut threads become infected by alcohol when using terminal sterilization. Coulthard and Sykes[3] reported that vegetative forms of bacteria are destroyed in a few minutes by concentrations over 60% but ethyl alcohol was impotent against bacterial spores.

In practice today, no reliance is placed upon the use of alcohol (dilute or strong concentrations) as a bactericidal agent for spore-forming organisms. If used at all, it is employed only against the weak resistant organisms and even here considering the technique when it is used (exposures of less than 5 minutes), the alcohol itself in all probability exerts little or no effect as a bactericidal agent.

Alcohol Employed Parenterally. Alcohol in various concentrations has been used externally; internally it has been consumed (by mouth) as an ingredient of various medicinal preparations or of liquors. More recently, however, parenteral therapy with alcohol has been advocated as an aid in the relief of pain and discomfort in a variety of abnormalities. Dogliotti[5] employed subarachnoid injections of absolute alcohol for the relief of peripheral pain in the lower part of the back, the pelvis and legs. Gilcreest and Mullen[8] advocated epidural and transsacral injections of alcohol for the relief of pain. Ruth,[21] Condamin and Arnulf,[2] Davis,[4] Newman,[16] Saltzstein,[22] Baker[1] and many other workers have employed parenteral alcohol therapy with apparent success. More recently, Pozzi and Belleli[19] employed intravenous injections of alcohol (10 cc. of 33% alcohol in a 45% solution of dextrose) and they noted an increase in the bactericidal power of the blood. Meynier[14] discusses the intraspinal (intrathecal) injections of alcohol for intractable pain in the pelvis and lower extremities.

Bacteria in Alcohol. Commercial alcohol has been generally accepted as bacteria-free. Only those workers who concern themselves with problems in disinfection and sterilization were familiar with the actual bactericidal properties of alcohol and had knowledge of the bacterial content of commercial alcohol. With the advent of the more frequent use of alcohol as a disinfectant in surgical procedures and its recent use for parenteral administration, several articles appeared in foreign publications concerning the germ content of commercial alcohol. Many devices and methods of sterilizing alcohol have been described.[13] Even in our own country some manufacturers have marketed sterilized absolute alcohol in ampules to be used for parenteral administration. Recently Kuhn and Dombrowsky,[12] Knorr,[10] and also Eschenbrenner[7] reported on the finding of bacteria, in particular spore-formers, in commercial alcohol. My attention was especially directed to the fact that Knorr[10] found more than half of the 38 samples of commercial alcohol (of different concentrations) laden with sporulating organisms. An examination of the American literature did not record findings of the bacterial content of commercial alcohols used in this country.

Experimental. A survey of the literature and personal conversations with many workers who employ injections of alcohol revealed that at least in this country the alcohol used in such injections is rarely redistilled, Berkefeld-filtered or otherwise treated as in sterilization techniques. Not one case of infection has come to the attention of the workers with whom I spoke, even though a total of several thousands of such injections were given by them. The alcohol used generally is the 95% (by volume) strength or the absolute product (dehydrated alcohol) obtained directly from the regular stock bottle in the drugstore or clinic, and the amount employed in each injection varies from 0.2 to 2 cc., the dose being usually 0.5 to 1 cc.

Accordingly 125 samples of commercial alcohol, consisting of 100 samples of 95% and 25 samples of absolute (dehydrated) alcohol were obtained. The samples were collected from retail pharmacies: from the drugstores, clinics, pathologic laboratories and operating rooms in large and small hospitals; from the bacteriologic, pathologic, chemical, operative pharmacy and botanical laboratories in teaching institutions; from containers in the offices of medical practitioners; and from stock cans, carboys and drums. The 25 absolute alcohol samples, though collected from 23 different places, were in all instances present in 1-pint cork-stoppered bottles. The 95% alcohol samples were obtained from all kinds of containers kept under varying conditions. There were small and large bottles, filled and partially filled, cork and glass-stoppered (some were not even stoppered), carboys, barrels and metal drums.

From each of the 125 samples, 1-cc. and 2-cc. portions were cultured aërobically, using at least 50 cc. of meat-infusion dextrose broth for each 1 cc. of alcohol to be cultured. A 2% alcoholic solution is not bacteriostatic and all kinds of spore-bearers were grown with ease in media of this alcoholic content. All cultures were incubated aërobically for 2 weeks at 37° C. and then for another 2 weeks at 20° to 22° C. Of the 125 samples, 10 of the absolute alcohol and 50 of the 95% alcohol samples which were cultured as above were also inoculated and incubated under anaërobic conditions. After 1 month incubation, none of the 125 samples revealed growth in the above medium when cultured in portions of 1 and 2 cc.

The following experiment revealed that spore-bearing bacteria could survive in 95% alcohol for varying periods of time. One-tenth cubic centimeter of a 1-week broth culture of *B. subtilis* was added to each 30 cc. of 95% alcohol placed in 6-ounce cork-stoppered bottles. A broth culture of *B. megatherium* was added in the same proportion to another bottle containing alcohol. Two 6-ounce sets were made, using two different strains of each organism, one in each instance as a check. The containers were stored at room temperature. At intervals of 3 to 4 days, 1-cc. and 2-cc. portions of the alcohol containing the added cultures were inoculated into meat-infusion dextrose broth, using at least 50 cc. of medium for each 1 cc. of alcohol cultured. The *B. megatherium* was found to survive in the 95% alcohol for a period of 88 and 96 days respectively, while 215 and 276 days respectively were required for the destruction of the two strains of *B. subtilis*.

Summary. One hundred and twenty-five samples of commercial ethyl alcohol, consisting of 100 samples of 95% alcohol and 25 samples of absolute alcohol, were obtained on the open market from as many different sources as possible. All of these, samples of ethyl alcohol produced in this country, were found to be free of bacteria and their spores. This is in contrast to reports from Europe where the commercial product was found to be contaminated frequently with spore-formers.

Alcohol (95%) did not kill *B. megatherium* and *B. subtilis* until after approximately 3 months' exposure in the first instance, and 7 and 9 months respectively were required for the destruction of the two strains of *B. subtilis* used in this experiment.

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NEGATIVE RESULTS OF RHUS ANTIGEN TREATMENT OF EXPERIMENTAL IVY POISONING.

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Rhus toxicodendron antigen intramuscularly and the tincture by mouth are frequently used in the treatment of ivy poisoning. Williams and MacGregor,[4] Strickler[3] and Bivings[1] have written encouraging papers on both prevention and treatment with these preparations.

Krause and Weidman,[2] however, in experiments on human volunteers, concluded that the preventive system of treatment of Strickler did not "prevent." They believed that the beneficial results which had been reported were dependent on and ascribable to the variable susceptibility of different individuals and the varying intensity of the irritant as applied at different times. They observed that transient pruritus ani appeared in the majority of those receiving preventive treatment. They were convinced that the pain at the sites of intramuscular injections outweighed any possible benefit in reducing the danger of future attacks of ivy poisoning. This paper deals with the therapeutic use of the antigen.

Methods and Materials. The plants employed for producing the dermatitis were identified as Rhus toxicodendron by the department of Botany of the University of Pennsylvania. A tincture was made by soaking the leaves, bark and stems for several days in pure grain alcohol. A 1 inch square of sterile gauze saturated with this tincture was applied to the skin for 24 hours. To prevent spread the area was covered with adhesive tape. Controls on the same subject were made, using a similar patch test with the pure alcohol.

The antigen used was supplied fresh by one of the large drug companies. The preparation and method of administration was that advocated by Strickler.[3] As recommended, 0.5 cc. was given intramuscularly; 24 hours later a second injection of 1 cc. followed; subsequently, at 48-hour intervals, one or two injections of 1 cc. were given.

Of 29 volunteers (medical students), 23 reacted with a typical eruption. Of these, 14 were observed as controls, while 9 received treatments. For uniformity, treatment was instituted as soon as vesiculation began to appear. Detailed records of each case were kept on uniform protocols, and conclusions as to results were made only after statistical analysis of the data.

Results. In the control group the duration of the dermatitis ranged from 3 to 16 days (average, 9 days). In the treated group the average duration was 11 days and in none had the symptoms entirely disappeared in less than 9 days. As for itching, it occurred in all cases and lasted in the control group for 3 to 4 days; in the treated group 3 days was the average, even omitting the solitary severe case with generalized pruritus of 9 days' duration.

The majority of the volunteers experienced painful reactions at the site of injections, lasting from 2 to 48 hours. Among these students the consensus was that those who received treatment experienced the greater discomfort. In 1 individual, nausea followed after each injection. Generalized pruritus occurred in one who had received 3 injections.

Summary and Conclusions. 1. Rhus antigen was tested for curative power on 9 volunteers, 14 acting as controls.

2. The antigen injection intramuscularly at the onset of the eruption did not appear to shorten the course of the dermatitis. Its effect on the intensity of the pruritus was slight, if any.

It appears, then, that the routine use of the antigen treatment of ivy poisoning is not warranted. The discomfort and expense, upwards of $3.00 for 4 injections, overbalance the very questionable therapeutic effectiveness.

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THE URINARY OUTPUT OF VITAMIN C IN ACTIVE TUBERCULOSIS IN CHILDREN.

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Since 1928 when Szent-Gyorgyi[3] isolated hexuronic acid from the cortex of animal adrenals, brilliant investigations have added much to our knowledge of vitamin C. Its chemical structure and properties, now well known, have recently been reviewed in detail by Wright and Lilienfeld.[13] While the part played by vitamin C in human physiology is still incompletely understood, it is definitely known that it is essential for the maintenance of normal capillary permeability. Wolbach and Howe[12] in their studies concluded that a lack of vitamin C results in an "inability of the supporting tissue to produce and maintain intercellular substance." They further postulated that this defect also holds true for the connective tissue of the teeth. Schroeder[7] is of the opinion that hypovitaminosis C prolongs the coagulation time of the blood, diminishes the number of blood platelets and causes a decrease in the hemoglobin. Among positive effects attributable to the vitamin are improvement of appetite, and stimulation of growth and glandular functions. More recent investigations suggest that it is also involved in defensive mechanisms against bacterial toxins.

Studies of the rôle of vitamin C in infectious diseases are comparatively few. However, sufficient data have accumulated to suggest that a deficiency may occur in various infectious states. Wilkinson and Ashford[11] found this in 3 cases of Addison's disease and point out a possible relationship between vitamin C deficiency and pathologic pigmentation. The deficiency they observed in general hospital cases was attributed to an inadequate intake of the vitamin. Harris *et al.*[6] believe that hypovitaminosis C may occur in any type of pyrexia and toxemia. Abbasy *et al.*[2] found acute and chronic juvenile rheumatism associated with a vitamin C deficiency and state that these children require a greater amount of the vitamin in their diet than do normal children. Grunke and Otto[4] found that diphtheria was always associated with a low urinary excretion of ascorbic acid. They made similar observations in scarlet fever, measles, bacillary dysentery, paratyphus, erysipelas and colitis. However, the upper level of what these investigators consider low elimination figures (15 to 20 mg. /24 hours) falls within the normal excretory level of most workers.

Since many investigators have found varying forms of hypovitaminosis C associated with toxemias, it is reasonable to expect a similar occurrence in active tuberculosis because of its chronicity and prolonged toxicity. The literature presents many suggestions of vitamin C deficiency in tuberculosis, but there is little actual evidence of studied cases. Schroeder[7] believes that tuberculosis is associated with increased vitamin C metabolism, as manifested by decreased elimination of ascorbic acid in the urine and Widenbauer[10] made similar observations. In an attempt to obtain further data, the authors have routinely determined the urinary output of all cases of active tuberculosis in the children's wards of the Tuberculosis Service of the Buffalo City Hospital.

Method. The 24-hour urinary output of vitamin C was determined by a modification* of the dichlorophenolindophenol technique of Harris and Ray.[4,5] From 5 to 15 cc. of the 24-hour sample is brought to a total volume of 15 cc. with water and then adjusted to an approximate pH of 4.7.† Its reducing power is estimated by rapid titration with Tillman's reagent,‡ the endpoint being a reddish violet tinge persisting for at least 15 seconds.

The standard daily diet served these children was one considered high in vitamin C, containing 55 to 65 mg. per 24 hours. The coöperation of the nursing staff and the children was such that we have no hesitancy in stating that the full amount was taken daily. As controls, were 25 normal children on the same approximate diet.

Results. Of the 39 cases examined it will be noted that, with the exception of Cases 11 and 32,§ the highest excretion was 8.5 mg. The lowest was 2.8 mg. and the average of the 37 cases was 5.7 mg. This was distinctly below the control group of 25 normal children, the highest being 40.2 mg., the lowest 22.5 mg., and the average 29.2 mg.

Discussion. The low excretory level of 5.7 mg. in the tuberculous children falls definitely below 10 to 15 mg., the figure generally accepted as the minimum normal level. On the other hand, the control group average of 29.2 mg. was definitely above the latter figure, indicating that the diet was more than adequate for a normal child. This finding agrees with that of other investigators, Van Eekelen[9] for example, considers 50 to 60 mg. adequate for a body weight of 70 kg.

Such a low level of excretion in the tuberculous children would seem to point to increased destruction of the vitamin in the body. The exact mechanism, if such a condition exists, is not known. It must be remembered that vitamin C is thought to have its physiologic effect by a process of alternate reduction and oxidation, the reaction being apparently reversible. However, it is only in the reduced form that the vitamin can be assayed. This is done by measuring its reducing power against various oxidizing solutions. How then can we state that decreased urinary excretion of the vitamin in the reduced state indicates hypovitaminosis? This can be best answered by correlating clinical and laboratory data. Typical examples of gross vitamin C deficiency such as scurvy are found associated with greatly lowered excretion of the reduced vitamin in the urine. The administration of the vitamin in sufficient quantities cures the patient clinically. At the same time the urinary output of the reduced vitamin is elevated to normal limits. This increased elimination suggests "saturation" of the tissues, the excess being spilled over into the urine. Such observations seem to justify a linkage of decreased urinary output of the vitamin in the reduced form with hypovitaminotic states.

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* Described by T. S. Bumbalo in thesis for M.S. (medicine), to be published.

† Two to three drops of 1 to 1000 Congo-red are placed in the depressions of a color plate. Ten per cent acetic acid is then added to the diluted urine in amounts of 0.10 cc. until a drop of the sample turns the indicator a purplish blue.

‡ Tillman's reagent. 20 mg. of 2:6 dichlorophenolindophenol is dissolved in 70 to 80 cc. of warm H_2O—cooled and made up to 100 cc. in a volumetric flask. One cc. is equivalent to 0.092 mg. of vitamin C as determined by our standardization. The solution, if kept in a dark bottle at 5 to 10° C., will not deteriorate appreciably for 7 days.

§ Cases 11 and 32 were receiving additional vitamin C from fresh fruit brought in by their visitors.

Our findings in all 37 of the tuberculous group points definitely to hypovitaminosis, especially when one considers that the same diet in normal children resulted in comparatively high excretory levels. As previously mentioned, similar hypovitaminotic states are encountered in other acute and chronic infections. The cause for such deficiencies, on a vitamin C adequate diet, is not altogether understood. Such terms as "increased vitamin C metabolism" are used, but do not seem to afford a satisfactory explanation. It is possible that hypovitaminosis C may exist in many cases of active tuberculosis in both children and adults, due to inadequacy of diet. As seen in our series the large daily intake of 55 to 65 mg. was definitely insufficient. At the present time we are conducting studies to determine the approximate number of milligrams necessary for the establishment and maintenance of saturation in these children.

TABLE 1.—URINARY VITAMIN C OUTPUT IN TUBERCULOSIS.

Case number.	Case.	Age.	Color, sex.	Type of tuberculosis	Nutrition	Urine output 24 hours (cc)	Vitamin C output 24 hours (mg).
1	L. B.	13	W. F.	Pulmonary, with cavity	Good	2000	8.4
2	J. B.	9	C. M.	Childhood, pleurisy with effusion	Fair	850	4.5
3	U. F.	7	C. M.	Pulmonary, with cavity	Fair	700	4.7
4	F. E.	13	C. M.	Pulmonary, with cavity	Poor	1000	2.8
5	T. C.	14	W. F.	Pulmonary, with peritonitis	Good	600	4.8
6	K. C.	13	W. F.	Adenitis	Good	900	8.1
7	R. M.	14	W. F.	Pulmonary, with cavity	Poor	1000	1.2
8	R. M.	14	W. M.	Pulmonary, with cavity	Poor	750	4.0
9	R. R.	11	W. M.	Spine	Fair	1050	8.4
10	J. Y.	11	W. M.	Spine and pulmonary	Fair	950	3.2
11*	J. C.	10	C. M.	Childhood	Poor	600	20.1
12	B. G.	9	W. F.	Childhood	Fair	900	7.2
13	L. B.	13	W. F.	Pulmonary, with cavity	Fair	940	3.2
14	S. M.	8	W. M.	Left hip	Poor	1100	8.4
15	B. F.	5	W. F.	Pulmonary	Good	650	6.5
16	M. B.	6	W. F.	Pulmonary	Fair	500	5.8
17	T. K.	11	W. M.	Spine and right knee	Poor	750	5.5
18	R. M.	4	C. M.	Pulmonary	Poor	100	3.9
19	W. M.	11	C. M.	Pulmonary	Poor	1000	4.5
20	D. C.	12	C. M.	Right knee	Good	750	7.5
21	C. D.	10	W. M.	Left knee	Poor	625	5.6
22	H. M.	11	C. M.	Childhood	Fair	1250	5.3
23	W. F.	10	C. M.	Pulmonary	Fair	850	4.2
24	J. J.	8	C. M.	Left knee	Good	520	8.3
25	H. B.	12	C. M.	Pulmonary	Good	850	4.5
26	F. T.	9	W. M.	Right knee	Fair	1150	6.8
27	R. B.	11	W. F.	Pulmonary	Fair	1000	7.3
28	J. N.	12	W. M.	Childhood	Good	1200	7.5
29	J. Y.	13	W. M.	Spine	Poor	1000	3.2
30	E. H.	13	C. F.	Childhood	Fair	550	6.7
31	W. M.	9	W. M.	Pulmonary	Poor	750	8.2
32*	D. N.	9	W. F.	Childhood	Fair	1050	45.0
33	C. P.	10	W. M.	Pleurisy with effusion	Poor	1100	5.8
34	B. O.	13	W. F.	Left hip	Good	800	6.5
35	C. G.	3	C. F.	Miliary	Poor	350	2.7
36	E. E.	7	C. F.	Childhood	Good	675	6.8
37	R. M.	10	W. F.	Childhood	Fair	1750	5.0
38	C. J.	5	C. M.	Childhood	Good	575	6.0
39	A. B.	13	W. M.	Pulmonary, with cavity	Fair	1250	3.8
							Average 5.7 mg.

* Received additional vitamin C from fresh fruit brought in by their visitors.

Summary and Conclusions. 1. All 37 cases in the children's wards of the Tuberculosis Service of the Buffalo City Hospital showed a decreased urinary excretion of vitamin C (reducing power as determined by the dichlorophenolindophenol method) on a daily ration of 55 to 65 mg. daily. Their average was 5.7 mg. as compared with a 29.2 mg. average of the 25 normal control children. In general, the greater the severity of the tuberculous process, the lower the excretory figures.

2. All 37 cases must be classified as subclinical hypovitaminosis C. The administration of the vitamin in amounts sufficient to produce saturation, and consequently a normal urinary output, is indicated.

3. The usual type of diet is inadequate for tubercular patients. Supplementary addition of the vitamin would seem advisable.

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FURTHER NOTE ON CARCINOMA OF THE BREAST IN ONE OF HOMOLOGOUS TWIN SISTERS.

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As the twin referred to in my article in this *Journal* (190, 331, 1935) had at that time only been observed by me for 2 years without developing carcinoma of the breast, like her twin sister, it seems desirable to add a further note at this time. It can now be said that over a period of 8 years since the appearance of carcinoma in the twin no evidence of carcinoma in the sister has become manifest. The possibility that the twins are not really homologous cannot be completely disproved, in fact would not necessarily be disproved if an apparently single placenta had been found. However, the fact that both persons are of the same sex, and of the same general appearance and constitution, would make it at least probable that they are homologous.

BOOK REVIEWS AND NOTICES.

Pediatric Dietetics. By N. Thomas Saxl, M.D., F.A.C.P., F.A.A.P., Associate and Lecturer in Diseases in Children, New York Post-Graduate Medical School, Columbia University; Assistant Attending Physician, Babies' Ward, New York Post-Graduate Hospital, etc. Foreword by Adolph G. DeSanctis, M.D., F.A.A.P., Director of Pediatrics at the New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 565; 57 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1937. Price, $7.00.

This book is filled, perhaps overfilled, with data and advice concerning the composition, classification and metabolism of children's foods, infantile digestion, maternal nursing, artificial infant feeding, diets, recipes, and menus. Its largest part is organized into a series of chapters on the dietetic management of the important pediatric diseases, a number of chapters being contributed by collaborating specialists. A thick appendix contains height-weight tables, physiologic data, well-selected bibliographies and long tables on the calorie, vitamin and mineral content of foods. The style is readable, the typography good and the index comprehensive.

The presentations are sound, conservative, and usually good, expressing in the main standard pediatric practices. Fads, fancies and freak diets are at a minimum, although the reader might prefer less emphasis on the proprietary infant-feeding preparations. One would like to see also some discussion of soft curd, vitamin D fortified, and other market milks, lead poisoning, raw banana feeding, flash pasteurization, and especially the splendid work of the American Medical Association's Council on Foods. All in all, however, the book should prove useful to the practitioner who desires a one-volume treatise on practical pediatric dietetics.

I. W.

Clinical Endocrinology. By Samuel A. Loewenburg, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia; Assistant Visiting Physician, Philadelphia General and Northern Liberties Hospitals and Eagleville Sanatorium for Consumptives, etc. Foreword by Hobart A. Reimann, M.D., Professor of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia. Pp. 825; 184 illustrations, 37 charts and tables. Philadelphia: F. A. Davis Company, 1937. Price, $8.00.

In this book the author has followed the conventional outline of a medical text. There is an introductory chapter which stresses history taking and physical examination in the endocrinopathies. There follow chapters on the pineal, pituitary (anatomy, physiology and pathology), diseases of the pituitary thyroid, parathyroid, pancreas, adrenals, female and male gonads, undetermined endocrine activities (properly brief) and a final chapter on the significance of laboratory findings. Each chapter follows, for the gland considered, the outline, history, anatomy, physiology, pathology, diagnosis and treatment. Remarks on endocrine interrelationships are included in several chapters. This outlins the scope of the book, and its purpose, namely, the clear presentation of the diseases of the ductless glands.

This purpose has been fulfilled by the concise and fluent writing and the orderly arrangement of the material. An underlying regard for general medicine is evident throughout, especially in the sections on differential diagnosis. The inclusion of tables of body weights and measurements, laboratory data in normals, etc., will save time for the reader. The sections on treatment are to be highly commended. Fads are avoided, a large number of alleged remedies are discarded on the grounds of experience and the judgment of a sound and practical clinician is apparent. The book is supplied with good illustrations.

In such a large subject omissions or minor errors will occur and each reader will note these for himself. The Reviewer failed to find any mention of Crooke's work on the hyaline degeneration of the basophilic cells of the pituitary—a work of clinical pathologic coördination which should appeal to all clinicians. Perirenal air injection for the Roentgen ray diagnosis of adrenal tumors, and the use of low sodium diets in the diagnosis of Addison's disease were not mentioned.

The glucose-tolerance test of 0.8 gm. per pound (=1.75 gms. per kg.) is described. This should be per pound of *ideal* weight in fairness to the functioning tissues of the obese or edematous. Perhaps the English system of a standard dose of 50 to 100 gms. is as satisfactory as any for routine use. The bitterling test is described (correctly) as a measure of estrogenic substances, but since it also appears to measure male sex hormones and perhaps other sterols, its insertion in a text might be postponed.

The last comment merely indicates the problem of deciding when an up-to-date fact is established, and no work on endocrinology can escape this difficulty. The author has avoided controversial writing and clinically his conclusions are correct. In adopting this worthy impartiality, however, there is a certain lack of stimulating or advanced ideas. Thus the possible rôle of the pituitary in thyroid disease is referred to but not discussed with the emphasis which even conservative authorities are giving this subject today.

These comments do not prevent the Reviewer from agreeing with Dr. Reimann's statement in the Foreword that the author's experience in teaching, as presented in this book, will be of real value to students and practitioners.

F. L.

A TEXT BOOK OF MEDICINE. By American Authors. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital, New York City; Associate Editor for Diseases of the Nervous System; and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Neurology, Cornell University Medical College; Director, Department of Neurology, Bellevue Hospital, New York City. Pp. 1614; 42 illustrations. Fourth edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1937. Price, $9.00.

THE popularity of this well-known text is demonstrated by the fact that the fourth edition appears only ten years after the first. The editor states that he has tried to bring every subject up to date and thereby give the student an authoritative presentation of present-day internal medicine. Several "new" topics—at least they were not included in previous editions —have been introduced. A retiring age for contributors has been established so that the present edition contains an unusually large number of new treatises on old subjects.

In the preface to the first edition, the editor stated that the rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field. He has therefore divided the field among 130 contributors. Most of these contributors are recognized authorities on the subjects they discuss. Consequently the percentage of erroneous statements, including the propagation of traditional misbeliefs from older texts is at an unusually low level. Many of the treatises are excellent although some others are dull and difficult to read. From this point of view there are all gradations from good to bad.

On the whole, this is a very useful textbook of medicine and can be heartily recommended to students. The Reviewer feels that every student whose ambitions soar beyond the mere passing of examinations should equip himself with at least two textbooks of medicine. This book should be one of the two. C. W.

A Textbook of the Practice of Medicine. By Various Authors. Edited by Frederick W. Price, M.D., C.M., F.R.C.P., F.R.S. (Edin.), Consulting Physician to the Royal Northern Hospital; Senior Physician to the National Hospital for Diseases of the Heart, London, etc. Pp. 2038; 112 illustrations. Fifth edition. New York: Oxford University Press, 1937. Price, $12.50.

Five editions and a total of 14 printings since 1922 are ample proof of the popularity of this excellent British text. The work of 28 contributors, it shows the uniformly high standard of excellence of its various sections which such multiple authorship can achieve more easily than can a single author. At the same time, good editorial supervision has taken care of covering all topics, with proper emphasis and without duplication. The work differs from American texts in its inclusion of sections on tropical diseases, psychiatry and dermatology, the latter of somewhat questionable value in the absence of illustrations. The index is exceptionally good. R. K.

Personality and the Cultural Pattern. By James S. Plant, M.D., Director, Essex County Juvenile Clinic. Pp. 432. New York: The Commonwealth Fund, 1937. Price, $2.50.

In this thought-provoking book the author presents the method of attack on personality problems which he has developed and used for 15 years in the several institutions of Essex County. In addition, he advances his philosophy of mental hygiene—or prophylactic psychiatry—which is somewhat unique since it emphasizes the dynamic effect of environment and the whole social order upon the individual personality—especially in childhood.

In fair and logical exposition he analyzes the approaches offered by the mental hygiene methods customarily used, formal psychiatric methods employed in clinics, and psychoanalysis. Except in obscure cases of mental disease in more advanced age groups, he believes that the latter two procedures are either too time-consuming and too highly formalized or even entirely unfited for the early variations of personality which occur so frequently in childhood. The author prefers to build up a system of mental hygiene based on recognition and study of the "casual breakdown." To accomplish this adequately he suggests that such cases be handled in informal clinics attached to courts' schools, factories and churches. He visualizes the highly trained psychiatrists as organizers and teachers rather than as workers in the units. He believes that in this way the relations of society, environment and the individual personality, together with their effects on each other are studied and integrated better.

This whole presentation together with the author's observations on our whole social order should prove to be of great interest to physician, sociologists, ministers, educators and officials in our criminal and juvenile courts. The author's methods of attack in the hands of those who have had the opportunity to observe them in his clinics should prove to be a contribution to the study of childhood behavior and to the development of sound personality patterns. E. T., Jr.

A BRIEF RULE TO GUIDE THE COMMON–PEOPLE OF NEW-ENGLAND. How to Order Themselves and Theirs in the Small Pocks, or Measels. [First published in 1677–78, reprinted in 1702 and 1721–22.] By THOMAS THACHER. Facsimile reproductions of the three known editions with an Introductory Note by HENRY R. VIETS, M.D. Pp. 54; illustrated. Price, $1.50.

A DISCOURSE UPON THE INSTITUTION OF MEDICAL SCHOOLS IN AMERICA. [Reprinted from the first edition, Philadelphia, 1765.] By JOHN MORGAN. With an Introduction by ABRAHAM FLEXNER. Pp. 63; 1 illustration. Price, $2.00.

ADAPTATION IN PATHOLOGICAL PROCESSES. [Reprinted from Transactions of the Congress of American Physicians and Surgeons, 1897, vol. IV, pp. 284–310.] By WILLIAM H. WELCH, M.D., LL.D. With an Introduction by DR. SIMON FLEXNER. Pp. 58; 1 illustration. Price, $1.50.

The above 3 books (publications of the Institute of the History of Medicine, The Johns Hopkins University, Fourth Series, Bibliotheca Medica Americana, vols. I, II and III, respectively.) Baltimore: The Johns Hopkins Press, 1937.

AMONG the several contributions that our only American Institute of the History of Medicine makes to medical history are its five series of publications: 1, Monographs; 2, Texts and Documents; 3, Noguchi Lectures; 4, "Bibliotheca Medica Americana;" and 5, the *Bulletin* of the Institute. The 3 volumes listed above are the first 3 of the fourth series, reprints of important medical Americana, with introductory historical, biographic and bibliographic sections. These sections may occupy but a few pages, as in the Morgan reprint; or far surpass the original text in size, as in the case of Thacher's Brief Rule. In the case of the Brief Rule, in fact, the original text does not even appear listed in the Table of Contents, as its 3 editions occupy 16 pages of illustrations only.
E. K.

AN OUTLINE OF GENERAL PHYSIOLOGY. By L. V. HEILBRUNN, Associate Professor of Zoölogy in the University of Pennsylvania. Pp. 603; 122 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, $5.00.

THE nature of the subject discussed in this book is very clearly outlined in the introductory chapters. General physiology is defined as the science which deals with all forms of living material. The general physiologist believes that all life has something in common; his search is often for the most common denominator of living processes; his aim is to discover, so far as possible, the nature and mechanism of living matter. Professor Heilbrunn points out that modern progress in biology has resulted from the fortunate realization that living things, no matter how diverse they appear in externals, are fundamentally much alike; and it is quite certain that much of the hope of the future lies in the possibility of using simpler types of protoplasm in order to discover the general characteristics of living things.

The early chapters of the book deal briefly with the structural, physical and chemical properties of living systems. Then follows a more detailed survey of the activities of living things: general metabolism, nutrition, digestion, respiration, secretion, excretion. In further chapters are then taken up the energy output due to these activities, the production of mechanical energy, of heat, electricity and light. The environment and the effect of environment is next considered, and in connection with this the adaptability to changes in the environment. This logically leads to a discussion of the reaction to various stimuli, one of the most important of the properties of living system. The book concluded with chapters on reproduction and on senescence.

Throughout the book the author has directed attention to the original literature, to the sources of information. The interested student or research worker will find this bibliography very helpful, and judiciously selected.

Professor Heilbrunn's book can sincerely be recommended to the physician and the biologist who would gain a broad survey of the manifestations of life, and the undergraduate as a well written presentation of a subject which is, in truth, the foundation of all the biologic sciences.

B. L.

DIE STERNALPUNKTION ALS DIAGNOSTISCHE METHODE. By PROF. DR. HANS SCHULTEN, Hamburg-Eppendorf Pp. 82; 2 illustrations by Gisela Krämer; 16 plates in color. Leipzig: Georg Thieme, 1937. Price, RM. 18.

THIS little monograph, dealing with biopsy of the sternal bone marrow as a diagnostic procedure, is the best of its kind that has appeared thus far. It is notable especially because of the excellence of color plates which reproduce faithfully the appearance of blood cells and their progenitors as seen in normal and various disease states. The author discusses technical methods, cytologic features of the several developmental series and a practical scheme of hemopoiesis. Over half of the test is devoted to a special section in which bone marrow findings (his own and those of others) in disease of the blood-forming organs are concisely described. Six pages of references furnish a fairly comprehensive bibliography.

The puncture and aspiration method of obtaining marrow was employed (which the Reviewer regards as inferior to the trephine method), but the author is careful to point out possible fallacies and reasons for discrepancies in differential counts.

American medical publishers can well take note of such paper-backed volumes as a relatively inexpensive but quite adequate medium.

R. C.

CLINICAL ALLERGY. By LOUIS TUFT, M.D., Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital; Associate in Immunology, Temple University School of Medicine; Director of Laboratories, Pennsylvania Department of Health, Philadelphia. Introduction by JOHN A. KOLMER, M.D., DR. P.H., D.Sc., LL.D., L.H.D., Professor of Medicine, Temple University; Director of Research, Institute of Cutaneous Medicine, Philadelphia. Pp. 711; 82 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, $8.00.

THE past 25 years have seen an amazing increase in our knowledge of the field of human hypersensitiveness. This information is found in a rapidly growing literature, much of it speculative and controversial. Some major and detailed texts have been written primarily for those who make this field their chief interest. A number of manuals have also been published for the guidance of patients. With the exception of Vaughn's book (and even this was primarily written with the patient in view) nothing has appeared for the benefit of the student and general practitioner. The current medical texts, even the systems, are woefully deficient in this regard. Dr. Tuft's book, written for the practitioner and student, therefore fills a real need. In fact, it overfills it, for it has grown to proportions probably beyond those originally intended by the author. This, however, is the practitioner's, if not the student's, gain. The subject matter is exceedingly well arranged and well presented. The first section considers the fundamental principles of allergy and anaphylaxis, including diagnosis and treatment. The second section discusses clinical allergy from the standpoint of etiologic agents (*e. g.*, allergy to serum, to drugs, foods, pollens, bacteria and physical agents). The third section takes up the clinical

manifestations of allergy, notably asthma, hay fever, gastro-intestinal allergy and migraine. The allergic skin conditions are described in the fourth section, together with chapters on allergy in children and in relation to certain other medical specialties. Of particular value and interest is the appendix with its descriptions of methods, lists of allergens, diets and recipes. There is a considerable bibliography, conveniently arranged by subjects, which especially the young allergist will find helpful. The book is heartily recommended.
R. K.

BIOLOGICAL TIME. By P. LECOMTE DU NOÜY, Chief of the Division of Molecular Biophysics, Pasteur Institute, Paris; formerly Associate Member of the Rockefeller Institute. With a Foreword by ALEXIS CARREL, M.D., Rockefeller Institute for Medical Research. Pp. 180; 31 illustrations. New York: The Macmillan Company, 1937. Price, $2.00.

DURING the World War the author studied with Carrel the rate of healing of wounds, work which was published and obtained world-wide recognition. In the present volume the author takes the reader "behind the scenes" of this investigation, informally discusses the origin of the problem in the hospitals of France, how difficulties arose and were met. He goes through the successive steps in mathematical analysis and shows how equations were fitted to the data. It was found that a man of 40 takes nearly twice as long, for example, to cicatrize a wound as a man of 20; a man of 50 four times longer than a child of 10. A similar effect of age was reported by Carrel, who found that fibroblasts in tissue culture grow much faster in the serum of a young chicken than in that of an old one.

From these two instances the author makes the generalization that the tempo of life is very rapid in childhood and progressively declines with age (though the author concedes that not all biologic phenomena are slowed up by age in the same proportion as cellular activity). From these considerations he develops the conception of "physiological time" as opposed to sideral time. The year seems much longer to the child than to the adult. Everything occurs "as if sideral time flowed four times faster for a man of fifty than for a child of ten." Therefore "when we take physiological time as a unit of comparison physical time no longer flows uniformly."

The Reviewer is not qualified to criticize the author's philosophic discussion of time, and possibly for this reason, found the earlier part of the book dealing with the author's experiments much more interesting.
M. McC.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. X. Tagung zu Bad Nauheim vom 13.–14. März, 1937. Hauptthema. Kreislauf und Innere Sekretion. Herausgegeben von PROF. DR. EB. KOCH, Bad Nauheim. Pp. 320; 140 illustrations. Dresden: Verlag von Theodor Steinkopff, 1937. Price, Rm. 15.

OF the 35 contributions to this session, 16 bear on the main theme—the circulation and internal secretion. Beginning with an address by Sir Henry Dale on vasodepressor substances, such topics were presented as Adrenalin as a Circulatory Hormone (H. Rein-Göttingen); the Hypophysis and the Circulation (F. Schellong); Hormones and Circulation in Relation to Pregnancy (W. Haupt); the Circulation in Disturbances of Blood Sugar Regulation (M. Burger); the Circulation in Disturbances of the Thyroid (G. W. Parade) and so on. One can safely say that the usual high standard of these Proceedings is maintained in the present volume.
E. K.

DIE HOMÖOPATHISCHE BEHANDLUNG DER AUGENKRANKHEITEN. By DR. KARL ERHARD WEISS, Augenarzt in Stuttgart. Pp. 182. 2 Durchgesehene und Verbesserte Auflage. Stuttgart: Hippokrates-Verlag G.M.B.H., 1937. Price, paper, Rm. 6.80; Bound, Rm. 8.00.

THE first part of this book is an alphabetical list of homeopathic remedies, which may be used in the treatment of eye diseases. Most of these have long since disappeared from the pharmacopœia. The second part deals with various diseases of the eye and suggests the use of the remedies mentioned in the first half. It is rather interesting to find a book advocating the use of remedies whose pharmacodynamic action has been demonstrated to be *nil*, such as gelsemium, oleander, pulsatilla, and so on.

F. A.

ALLERGY. ITS PRACTICAL APPLICATION. Expressly Prepared for Physicians and Students of Medicine, Containing Practical Points Necessary for the Care of Patients with Asthma, Hay Fever, Urticaria, Eczema, and Other Allergic Conditions. By J. A. RUDOLPH, M.D., Associate Clinician in Charge to the Department of Allergy, Mt. Sinai Hospital; Consultant in Allergy, Cleveland Y. M. C. A. Pp. 224. Philadelphia: Dorrance & Co., Inc., 1937. Price, $3.00.

EXPRESSLY prepared for students and practitioners, the book to a large extent achieves this aim, in that it contains much practical information for the care of patients with allergic conditions. There is, however, much valuable space given to material not essential to the primary purpose of the book, for instance, the preparation of extracts, and unnecessarily detailed presentation of theories, often controversial. Errors and omissions are commonest in first editions, but some should not even occur in "firsts," such as the use of the word "intradermal," some of the prescription Latin, the statement that 90% of hay fever cases are of the fall variety, the failure to mention the use of adrenalin by atomizer. R. K.

THE HUMAN MIND. By KARL A. MENNINGER, M.D. Pp. 517; 17 illustrations. Second edition, corrected, enlarged and rewritten. New York: Alfred A. Knopf, 1937. Price, $5.00.

THE chapters of this popular volume discuss principles, personalities, symptoms, motives, treatments and applications. Personalities include those who tend to show difficulties when subjected to an additional strain; some, however, may lead successful lives: 1. Organic disease type—crippled personalities such as those redeemed from tuberculosis. 2. Hypophrenic type—stupid personalities. 3. Isolation type—lonely personalities which are of two sorts: "constitutionally" unsocial subjects who prefer to be left out of things, and the "wistful derelicts who long to dive into the stream." 4. Schizoid type—queer personalities, some of whom succeed because they are queer while others fail by reason of this. 5. Cycloid type—moody personalities. 6. Neurotic type—that large group of frustrated personalities that may become successful through struggle and compromise. 7. Antisocial type—perverse personalities that may show intelligence but are lacking in emotional and volitional functioning. The chapter on motives is chiefly concerned with psychoanalysis. There are minor errors and omissions: Peter the Great in one place is an epileptic and in another, a paranoiac; according to authorities he was neither, but was a pronounced *tiqueur*. Neglect to mention family care of mental patients which has definite advantages in selected cases. The author gives a non-technical, dramatic and at times delightful presentation of mental mechanisms that will appeal to lay readers and students. N. Y.

The Roentgenologist in Court. By Samuel Wright Donaldson, A.B., M.D., F.A.C.R., St. Joseph's Mercy Hospital, Ann Arbor, Mich. Pp. 230. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.00.

This book contains a wealth of sound advice concerning medical testimony. While the author primarily concerns himself with radiology and the law, it contains much of value to all members of the medical profession. With their medico-legal work on the increase, radiologists should find increasing use for this volume. It not only defines the radiologist's status as an expert witness, but cites numerous cases of importance in guiding radiologic testimony.

The chapter, "Doctor, Take the Stand," is well worthwhile reading by any physician who contemplates going into court as a witness for the first time.

P. H.

Tumors of the Nervous System. An Investigation of the Most Recent Advances. The Proceedings of the Association, New York, December 27 and 28, 1935. (Association for Research in Nervous and Mental Disease, Vol. XVI.) Editorial Board: Edwin G. Zabriskie, Angus M. Frantz, Clarence C. Hare. Pp. 493; 213 illustrations and 64 tables. Baltimore. The Williams & Wilkins Company, 1937. Price, $7.50.

Here are included tissue culture of gliomata, by R. G. Canti, J. O. W. Bland and Dorothy S. Russell; metabolism of brain, spinal cord and meningeal tissue, by S. Bernard Wortis; metabolism of brain tissue by Joseph Victor and Abner Wolf; antigenic properties of brain tumors, by Arthur Weil and Erich Liebert; effects of irradiation on gliomas, by C. H. Frazier and Bernard J. Alpers; gliomas of the central nervous system, by Arthur Elvidge, Wilder Penfield and William Cone; ependymomas, by James W. Kernohan and Eleanor M. Fletcher-Kernohan; meningiomas, by Joseph H. Globus; tumors and cysts of the cerebellopontine angle, by Leo Alexander; cerebrospinal fluid in brain tumor, by Frank Fremont-Smith; localization of brain tumors by tests of olfactory function, by Charles A. Elsberg; pneumencephalographic diagnosis of corpus callosum tumors, by Cornelius G. Dyke and Leo M. Davidoff; clinico-pathologic study of astrocytomas, by R. W. Waggoner and Konstantin Lowenberg; long postoperative survivals in cases of intracranial tumor, by Louise Eisenhardt; tumors of peripheral nerves, by Arthur Purdy Stout, George F. Laidlaw and Cushman D. Haagensen; tumors of peripheral nerve system, by Frank E. Adair and Jay McLean.

Appreciative discussion followed exhibition of tissue cultures of gliomata, with cinematograph demonstration of cells cultivated *in vitro*; however, the method was not offered as supplanting the histologic diagnostic procedure. Olfactory tests in localization of tumors brought out an interesting discussion; the author holds that smell is primarily physical, rather than chemical. The research association is to be congratulated upon having arranged a scientific program that elicited such an enlightening discussion.

N. Y.

Early Medieval Medicine. With Special Reference to France and Chartres. By Loren C. MacKinney, Ph.D., Professor of Medieval History, University of North Carolina. (Third Series, Vol. III. Publications of the Institute of the History of Medicine, The Johns Hopkins University. The Hideyo Noguchi Lectures.) Pp. 247; illustrated. Baltimore: The Johns Hopkins Press, 1937. Price, $2.75.

Few indeed are those students and writers who are thoroughly trained in both medicine and history; and as professional historians have for the most part concerned themselves very little with medical matters, we find that most essays in medical history emanate from the physician and all too often show the defects of the amateur. Though the author may be correct that it is harder to learn medicine than to learn history, still we are inclined to believe that the trained historian will do a better job with most medical subjects than *vice versa*. Certainly the little volume under consideration would support this view. Tracing in three lectures the progress of medicine through: 1, early medieval times, 2, Merovingian and Carolingian France, and 3, at Chartres in the 10th and 11th centuries, the author confirms the modern view that the Dark Ages, especially in their latter half, were far from pitch black in medicine as well as in general culture. In general, he steers a middle course, rejecting the claims both for a Carolingian medical renaissance and for a sharp decline of medicine in the next 2 centuries. As to Chartres, one has to be already a zealous supporter of that glorious cathedral to become enthusiastic about its Gerbert and its Filbert and the slender contributions of the cathedral school. The subject has been carefully prepared—the 284 textual notes occupy a good quarter of the book—and should now benefit many more than those who were fortunate enough to hear the third Noguchi lecture series. E. K.

EYESTRAIN AND CONVURGENCE. By N. A. STUTTERHEIM, M.D. (RAND.), ARTS (STAATS-EXAMEN., HOLLAND), Part-time Ophthalmic Surgeon to the Johannesburg School Clinic, Transvaal Education Department; late Assistant, Eye Clinic, University, Leyden. Pp. 89; 2 illustrations. London, H. K. Lewis & Co., Ltd., 1937. Price, 7s. 6d.

THIS book, of interest only to ophthalmologists, is a thesis on deficiency of convergence as a cause of eyestrain. The author's overenthusiasm for his point of view is best illustrated by the following quotation on page 45: "I have not yet met with a case of eyestrain where there was not a marked degree of asthenovergence." The treatment suggested is orthoptic exercises, which build up the convergence power. F. A.

THE MICROMOTIST'S VADE-MECUM (BOLLES LEE). A Handbook of the Methods of Animal and Plant Microscopic Anatomy. Edited by J. BRONTË GATENBY, M.A., PH.D. (DUBL.), B.A., B.SC., D.PHIL. (OXON.), D.SC. (LOND.), Professor of Zoölogy and Comparative Anatomy, Trinity College, Dublin; and THEOPHILUS S. PAINTER, A.B. (ROANOKE), A.M., PH.D. (YALE), Professor of Zoölogy, Texas University, U. S. A., with 10 COLLABORATORS. Pp. 784; 11 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $9.00.

A LARGE section on botanical microtomy technique has been added to this edition, in an effort to place on the shelves of botanists and zoölogists a book that will give each a chance to learn some of the methods of the other. New chapters have also been added on frozen sectioning and vital staining; many have been revised or rewritten. While it continues to be an excellent reference book on unusual methods, it is not as up-to-date on routine measures as might be hoped for. G. S.

THE THERAPEUTIC PROBLEM IN BOWEL OBSTRUCTIONS. A Physiological and Clinical Consideration. By OWEN H. WANGENSTEEN, B.A., M.D., PH.D., Professor of Surgery, University of Minnesota, and Surgeon-in-Chief, University of Minnesota Hospital. Pp. 360; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

PART I of this monograph, awarded the quinquennial Samuel D. Gross Prize in 1936 by the Philadelphia Academy of Surgery, considers the therapeutic problems of bowel obstruction, including the effects of distention, the recognition of bowel obstruction, the treatment of bowel obstruction, with a concluding chapter for summary and conclusions. In Part II are discussed the diagnosis, the picture presented by patients with bowel obstruction, guiding principles in treatment, choice of operation, operation and postoperative treatment. Part III deals with specific types of clinical obstruction.

It is little short of amazing that the author, whose fundamental researches in this field make him the best qualified American surgeon to discuss the subject, could have covered so much material in such a brief space. The important literature is briefly but adequately reviewed. All subject matter is clearly and concisely presented. The illustrations are excellent. No clinical surgeon can afford to fail to place this volume in his library; it fills a need and will long serve as a model for surgical monographs.

I. R.

A MONOGRAPH ON VEINS. By KENNETH J. FRANKLIN, D.M., M.R.C.P., Tutor and Lecturer in Physiology, Oriel College; University Demonstrator of Pharmacology; Assistant Director of the Nuffield Institute for Medical Research, Oxford. Pp. 410; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

IN the eager search for knowledge leading to control of arterial disease, it is not surprising that the veins, of less clinical importance, should have been comparatively neglected. Nevertheless, one is astonished to learn that this is the first English monograph on the subject and impelled to congratulate author and publisher on remedying the deficiency. The author, at the instigation of Professor Gunn, now Director of the new Nuffield Institute for Medical Research, has for several years been doing research work on the venous system. He now has integrated this with existing knowledge on the subject in a review primarily intended for others engaged in such studies, but useful of course, for the profession at large. Medical history, embryology (by Keith Richardson), anatomy—human and comparative—experimental physiology, pharmacology, and the clinic have all been drawn upon to give a complete picture of these structures and "the important parts they play in the harmonious interactions within the living organism."

E. K.

NEW BOOKS.

Erforschung und Praxis der Wärmebehandlung in der Medizin. Einschliesslich Diathermie und Kurzwellentherapie. 2. Frankfurter Konferenz für medizinisch-naturwissenschaftliche Zusammenarbeit am 13. und 14. Mai, 1937. Mit Unterstützung der Stadt Frankfurt a. M. Herausgegeben von DR. B. RAJEWSKY, o. Professor für physikal, Grundlagen der Medizin, Frankfurt a. M., und DR. H. LAMPERT, o. Professor für physikal, Therapie, Balneologie und Klimatologie, Frankfurt a. M. Pp. 185; 82 illustrations. Dresden: Theodor Steinkopff, 1937. Price, Paper, Rm. 8.; Bound, Rm. 9.50.

The Immunological Reactions of the Filterable Viruses. By F. M. BURNET, E. V. KEOGH, and DORA LUSH. (From the Walter and Eliza Hall Institute, Melbourne.) (Reprinted, with original page numbers, from "The Australian Journal of Experimental Biology and Medical Science," Vol. XV, Supplement to Part 3.) Pp. 136; 27 illustrations. Obtainable from The Librarian, University of Adelaide, Adelaide, South Australia, and H. K. Lewis Co., Ltd., London. Price, 10/–.

An Analysis of the De Generatione Animalium of William Harvey. By ARTHUR WILLIAM MEYER, Professor of Anatomy, Stanford University. Pp. 167; illustrated. Stanford University, Calif.: Stanford University Press, 1936. Price, $3.00.

Short Years. The Life and Letters of John Bruce MacCallum, M.D., 1876–1906. By ARCHIBALD MALLOCH. Pp. 343; illustrated. Chicago: Normandie House, 1938. Price, $3.50.

The Rôle of Chemiotaxis in Bone Growth. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S. (EDIN.). Pp. 59; 32 illustrations. London: Henry Kimpton, 1937. Price, 8/6.

Protoformotherapy in Treatment and Prevention. Fifteen Years of Research on New Scientific Bases of Therapeutics. By DR. N. E. ISCHLONDSKY, Paris. Extended edition of three successive lectures delivered before the Egyptian Medical Association at the University of Cairo in March, 1936, under the title: "The Internal Secretion of the Embryonic Tissues, its Biological Significance and its Importance in Practical Medicine." Pp. 237; 68 illustrations on 40 plates. London: Henry Kimpton, 1937. Price, 21/-.

A Dissertation on Acute Pericarditis. By OLIVER W. HOLMES. Introduction by JAMES F. BALLARD, Director, Boston Medical Library. Pp. 39. Boston: The Welch Bibliophilic Society, 1937. Price, $7.50.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynecology and Other Special Subjects. Vol. 5, Endoscopy of Respiratory Tract to Goitre. Under the general editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.), F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 683; 139 illustrations. London: Butterworth & Co. (Publishers), Ltd. Price, $12.00.

Love and Happiness. Intimate Problems of the Modern Woman. By I. M. HOTEP, M.D., with a Prefatory Note by DR. LOGAN CLENDENING. Pp. 242. New York: Alfred A. Knopf, 1938. Price, $2.00.

Fever Therapy. Abstracts and Discussions of Papers Presented at the First International Conference on Fever Therapy, College of Physicians and Surgeons, Columbia University, New York City, March 29, 30, 31, 1937. Edited by 9 Members of the American Committee. DR. WALTER M. SIMPSON, Dayton, Ohio, Chairman; DR. WILLIAM BIERMAN, New York City, Secretary. Pp. 483. New York: Paul B. Hoeber, Inc., 1937. Price, $5.00.

Neuland in der Heilkunde. By DR. HENRI HIRSCH. Pp. 87. Basel: S. Karger, 1937. Price, Fr. 3.20.

The new land lies in the recognition that health and disease are a function of the acid-base-equilibrium. This is "the base of all harmonious processes of the human organism," and its disturbance is "the base of all diseases." It is also the base of psychic processes. The pamphlet cannot be regarded as scientific. W. E.

Die Diffusionsanalyse am Blutplasmagel. Ein Neuer Weg der Blutforschung. By RUDOLF BUCHER. Pp. 123; 70 illustrations (30 in color). Basel: Benno Schwabe & Co., 1937. Price, Fr. 30.

Tissue Reactions in Bone and Dentine. A morpho-biological Study of the Formation and the Dissolving of Bone and Dentine. By ÅKE WILTON, M.D., Assistant Professor and Lecturer in Pathology at the Caroline Institute, Stockholm. Pp. 194; 64 illustrations and 5 plates in color. London: Henry Kimpton, 1937. Price, 15/-.

Physiologie de l'écriture Cursive. By DR. H. CALLEWAERT. Pp. 123; 57 illustrations. Bruxelles: L'edition Universelle, S.A., n.d. (No price given.)

The Physician's Business. Practical and Economic Aspects of Medicine. By GEORGE D. WOLF, M.D., Attending Otolaryngologist, Sydenham Hospital; Attending Laryngologist, Riverside Hospital, New York City. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. Pp. 384; 57 illustrations. Philadelphia: The J. B. Lippincott Company, 1938. Price, $5.00.

Man Against Himself. By KARL A. MENNINGER. Pp. 485. New York Harcourt, Brace & Co., 1938. Price, $3.75.

The Negro's Struggle for Survival. A Study of Human Ecology. By S. J. HOLMES, Professor of Zoölogy in the University of California. Pp. 296; 10 illustrations and 50 tables, also Appendix of 31 tables. Berkeley, Calif.. University of California Press, 1937. Price, $3.00.

Digestive Tract Pain. Diagnosis and Treatment, Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine. Harvard University; Physician, Massachusetts General Hospital. Pp. 152, 5 illustrations. New York: The Macmillan Company, 1938. Price, $2.50.

Surgical Pathology of the Diseases of the Neck. By ARTHUR E. HERTZLER, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kansas. Professor of Surgery, University of Kansas. Pp. 237; 206 illustrations. Philadelphia: J. B. Lippincott Company, 1937.

"To the Surgeon the neck is the most interesting region of the whole body. . . . A presumptive diagnosis is possible in the clinic and by the time the operation is finished very few lesions should be obscure. These few are found almost wholly in the affections of the lymph glands. Here also the pathologist finds his greatest difficulties. The present tendency to treat all lesions of the neck by irradiation without a definite pathologic diagnosis is to be deplored. What surgeons have learned is in grave danger of being lost by this practice. It is still the practice in my clinic to remove lesions by block dissection, thus insuring a positive diagnosis. This is then followed by irradiation if and when needed. Only by such a practice is it possible to know what has been cured, should permanent relief be obtained." (From the Author's Preface.)

Theoretical Principles of Roentgen Therapy. Edited by ERNST A. POHLE, M.D., PH.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wisconsin. Foreword by W. EDWARD CHAMBERLAIN, B.S., M.D., F.A.C.R., Professor of Radiology in the Temple University School of Medicine, Philadelphia. Pp. 271; 132 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

NEW EDITIONS.

Macleod's Physiology in Modern Medicine. Edited by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, with 8 Collaborators. Pp. 1051; 355 illustrations and 103 tables. Eighth edition St. Louis: The C. V. Mosby Company, 1938. Price, $8.50.

Approved Laboratory Technic. Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological. By JOHN A. KOLMER, M.D., DR.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine, Temple University; Director of the Research Institute of Cutaneous Medicine, Philadelphia, etc., and FRED BOERNER, V.M.D., Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Bacteriologist, Graduate Hospital, Philadelphia. Pp. 893; 380 illustrations and 12 colored plates. Second edition, rewritten, revised and reset. New York: D. Appleton-Century Company, Inc., 1938. Price, $8.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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SULPHANILAMIDE AND SIMILAR COMPOUNDS IN CHEMOTHERAPY.

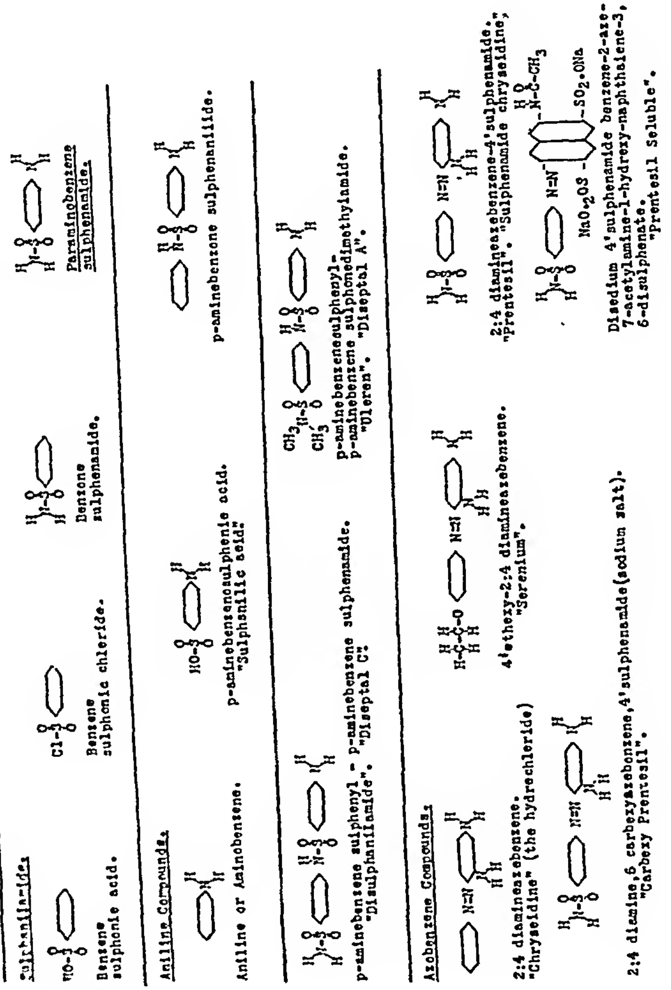
THE chemical compound, which started a most exciting series of researches in the field of chemotherapy, was synthesized by Mietzsch and Klarer[45] in 1932 and patented on Christmas Day of that year.[79b] It was the addition of the sulphonamide group to the molecule of the azo dye chrysoidine which resulted in producing the 2:4 diaminoazobenzene, 4′-sulphonamide, called for brevity's sake Sulphonamide chrysoidine, and known in the medical literature under the trade names "Streptozon" and later "Prontosil."

This compound was lifted out of the turmoil, caused by the appearance year after year of chemotherapeutic agents heavy with claims of antibacterial efficiency, when Domagk[45a] discovered a new principle. This consisted in the experimental observation that the *in vitro* antiseptic qualities of the azo dyes was reduced by the addition of the sulphonamide group; but, and this was the heart of the discovery, the therapeutic action *in vivo* was not only not reduced but when it was given to mice after intraperitoneal injections of fatal doses of hemolytic streptococci the mice did not die. The fine coöperation of the bacteriologists and the chemists led to the production of "Prontosil" and "Prontosil Soluble," and in the hands of clinicians there followed a series of dramatic curative results which recalled the early days of dioxydiamidoarsenobenzol—the "Ehrlich-Hata 606" or Salvarsan.

The earliest reports on the use of "Streptozon" were those of clinicians, and these appeared before the basic experimental work in Domagk's laboratory had been published. Of course, the compound had not been given out for trial in human infections without the necessary laboratory evidence, which had been obtained the same year as the synthesis of the drug, although this was not available to the general medical world until February, 1935.[45a] It is only of historic interest that Foerster[94d] in May, 1933, reported favorable results in a boy with widespread staphylococcus infection, that Grütz[94d] in 1934 had had good results in the treatment of different types of erythema, and that Veil[125] in the same year had noted a decrease in the sedimentation rate of the red cells and benefit in rheumatism when these cases were treated with "Streptozon."

Table I.

Structural formula of the chemical compounds referred to showing certain relationships.

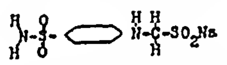

Sulphanilamides.
$HO-\overset{O}{\underset{O}{S}}$
Benzene sulphonic acid.
$Cl-\overset{O}{\underset{O}{S}}$
Benzene sulphonic chloride.
Benzene sulphonamide.
Paraminobenzene sulphonamide.
Aniline Compounds.
Aniline or Aminobenzene.
p-aminobenzenesulphonic acid. "Sulphanilic acid"
p-aminobenzene sulphonanilide.
p-aminobenzene sulphonyl - p-aminobenzene sulphonamide. "Disulphanilamide". "Diseptal C"
p-aminobenzenesulphonyl-p-aminobenzene sulphonedimethylamide. "Uleron". "Diseptal A".
Azobenzene Compounds.
N=N
2:4 diaminoazobenzene. "Chrysoidine" (the hydrochloride)
4'ethoxy-2:4 diaminoazobenzene. "Serenium".
2:4 diaminoazobenzene-4'sulphonamide. "Prontosil". "Sulphonamide chrysoidine".
2:4 diamine,6 carboxyazobenzene,4'sulphonamide(sodium salt). "Carboxy Prontosil".
NaO_2OS
$SO_2.ONa$
$N-C-CH_3$
Disodium 4'sulphonamide benzene-2-azo-7-acetylamino-1-hydroxy-naphthalene-3,6-disulphonate. "Prontosil Soluble".

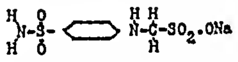
There was little or no interest aroused by these early reports; but in the early months of 1935 the tide began suddenly to rise, and by December, 1937, the writer of this review is all but overwhelmed by the flood of articles from clinicians, laboratory workers and chemists in all parts of the world, so that he must of necessity take note only of what he believes are the most important currents to which his attention has been drawn.

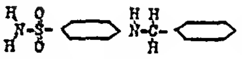
Chemistry. The chemical substances which are being developed in this field are referred to as chrysoidine, aniline, or more recently sulphanilamide derivatives. However, the compounds being tested are no longer confined to these derivatives since the stimulus of the experimental technical procedures, and the highly favorable results obtained in clinical cases has broadened the scope of this world-wide research. The structural formulas shown in the table are designed to indicate certain relationships among a number of substances which have already been reported and they may be helpful in following the present-day lines of research.

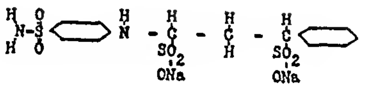
Table I (ctd.)

Compounds with additions to the amino radical of sulphanilamide.

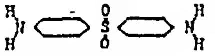

p-aminobenzenesulphonamide-formaldehyde sulphoxylate.

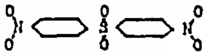

p-aminobenzenesulphonamide-formaldehyde bisulphite of sodium.

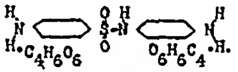

p-benzylamino-benzenesulphonamide. "Septazine".

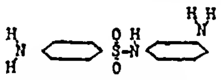

p-(γ phenyl-propyl-amino) benzene sulphonamide-α,γ. disulphonate of sodium. "Soluseptazine".

Sulphone Compounds (O=S=O or a compound of it with carbon).

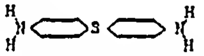

4:4 diaminodiphenyl-sulphone.

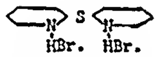

4:4 dinitrodiphenyl-sulphone.


4:4 diaminobenzene-sulphonanilide tartrate.

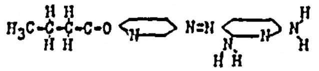

4:3 diaminobenzene-sulphonanilide.

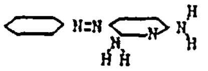
Sulphide Compounds.


4:4 diaminodibenzenesulphide. "Thioaniline".

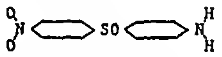

2:2 pyridylsulphide dihydrobromide.

Pyridine Azo Compounds.

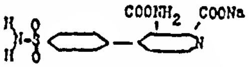

2, butoxypyridyl, 5, 5, azo, 2, 6 diaminopyridine. "Neotropin".

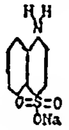

Benzene azo-2,6 diaminopyridine. "Pyridium".

Sulphoxide.*


4 nitro-4'aminodiphenyl sulphoxide.

Other Compounds.


p-benzenesulphonamide-pyridine- -carbonamide-d-carboxylate of sodium.


aminonaphthalene-4-sulphonate of sodium.

* Reported as a potent antiendotoxic agent (Gonococcus and B. aertrycke) Levaditi and Vaisman,. (Presse med. 45, 1371, 1937: Compt. rend. Acad. d. sc. 205, 1108, 1937).

Domagk,[45] Hörlein[79] and others have outlined the historic steps leading to the discovery of "Prontosil." The comparative failure of chemotherapy in bacterial infections had been outstanding, and the theory suggested was that the higher differentiation of protozoa and spirochetes rendered them more subject to chemical attack, in that certain functions essential to the life of these higher organisms could be affected with relative ease by a number of chemicals. A method suitable for testing such chemicals was the first necessity before progress could be made, and it must be recognized that success followed the trial and error system, and then only after a very long series of compounds had been tested. Here and there, more or less favorable results in experiments on animals narrowed the field until "Prontosil" was discovered with a low toxicity for animal tissue, a negative bactericidal effect *in vitro*, but a high therapeutic activity in artificially infected animals.

The publication of the chemical formula of "Prontosil," showing it to be a sulphonamide chrysoidine compound, naturally stimulated the search to discover what part of the molecule was chiefly responsible for the striking results. Many hundreds of substances have been studied by German, French, English and American investigators, and at the time of writing no fully satisfactory explanation has been reached, particularly because other compounds of different chemical structure have been found which give essentially the same type of results. Many of these have not had sufficient clinical application to permit evaluating them at present, but it should be emphasized that only the threshold of bacterial chemotherapy has been passed.

The first important step toward the chemical clarification was made by Tréfouël *et al.*,[155] when they found after testing a long series of substances that all those which gave favorable therapeutic results contained the para aminobenzenesulphonamide group, and that this compound by itself was as effective as the diaminoazobenzenesulphonamide compound. Further study by Fourneau *et al.*,[50] Buttle *et al.*,[30] Goissedet *et al.*,[63] Fuller,[56] Long and Bliss[94a] and many others, established the correctness of this discovery. At the suggestion of Fuller the name sulphanilamide, later adopted by the Council on Pharmacy of the American Medical Association,[1] has passed into current use and has largely, but unfortunately not completely, supplanted a long list of proprietary and other names among which those most commonly used have been "Prontosil Album" and "Prontolyn."

Sulphanilamide, as can be seen in Table 1, is derived from benzene sulphonic acid and its relationship to aniline and sulphanilic acid is also there indicated. The importance of the molecular structure has been shown by the authors referred to above. The para position of both the amine and the sulphonamide groups is essential for its effect in experimental infection. Buttle *et al.*[30] believed the amine attachment to the benzene ring was more important than the sulphonamide group alone, having found that the anilide derivative of sulphanilic acid was as active as the amide.

It is generally accepted that the azobenzene compounds, which are effective in experimental and clinical application, such as the sulphonamidechrysoidine ("Prontosil"), the carboxy modification (Carboxy-Prontosil) of Girard,[60] and the naphthalene compound ("Prontosil Soluble") owe at least the major part of their potency to the sulphanilamide group, which is set free on reduction of these compounds in the body. There is much evidence that this occurs both by finding the sulphanilamide in the urine and experimentally by reduction with a number of substances such as sodium formaldehyde "sulfoxalate,"[94a] stannous chloride[56] and sodium hydrosulphite,[11, 56] and cysteine hydrochloride.[19b] It has also been suggested[94a] that the streptococcus may cause reduction and a number have indicated that in the presence of inflammation such reduction may occur. Similarly, with the formaldehyde sulphoxylate (Bauer[128]) and the formaldehyde bisulphite[62] compounds, as well as with the more widely known "Septazine" and "Soluseptazine," the sulphanilamide group would appear to be readily released on reduction. The disulphanilamide ("Disulon"), Bauer,[128] (named Diseptal C or D.B.32)[79b] was a little more effective on streptococci given subcutaneously and less than one-fifth as acutely toxic as sulphanilamide in the hands of Rosenthal.[128] Hörlein[79b] said it was superior to sulphanilamide against staphylococcus as well as against gas gangrene in mice, and it has been used in treating human gonorrhea. The closely related dimethyl compound with the trade name "Uleron" (Diseptal A or D.B.90)[79b] has also been clinically tested in gonorrheal infections, as has a similar compound to the above but with a single CH_3 radical called Diseptal B (D.B.87). None of these three compounds, according to Hörlein,[79b] can be reduced to sulphanilamide.

All the substances containing the sulphanilamide radical do not act alike. They differ in toxicity, solubility, rapidity of excretion and in their effects on different bacteria. These differences are explained in a number of ways. The ease and rate of reduction of the more complex compounds may vary, so that the sulphanilamide released may be in a nascent or more potent state for longer periods in some than in others. The method of administration will alter the conditions favoring reduction, as will the presence of inflammation and other metabolic changes. The mere fact that the species of animal changes the relative efficiency of these drugs indicates the intricate factors which may be involved.

The second molecule set free when the azo or other linkage is broken must be considered in the final result produced by these compounds, and undoubtedly may alter the effects in the body. It has been recognized by a number of investigators[60a] that the effects of the different compounds do not run parallel with their sulphanilamide content. A mere glance at Table I will show the variety of secondary molecules which may be formed. Some of these may be changed or rendered inert in the body, but a great deal more work will be needed before the facts are fully known.

The large amount of evidence confirming the view that sulphanilamide is a remarkably efficient therapeutic agent against a variety of infectons makes it evident that equally extensive tests must be made with the growing number of other compounds which have given comparable results in experimental infections in animals. There are the sulphone compounds (diaminodiphenyl and the dinitrodiphenyl)[32] and the two diaminobenzenesulphonanilides,[161] the sulphide compounds, thioaniline[60b] and the pyridylsulphide,[88] the para benzenesulphonamide pyridine compound,[81] and the aminonaphthalene sulphonate.[30]* These various preparations do not contain the sulphanilamide radical. In the case of the first two sulphone compounds the conversion to sulphanilamide is highly improbable,[32] but these are effective in curing streptococcal infections in mice—the diaminosulphone in doses one hundred times less, and the dinitrosulphone in doses the same as sulphanilamide, the first being twenty-five times as toxic and the second less toxic for mice but not for rabbits.[32, 60b] The two anilide compounds[161] have a polyvalent action and have a low toxicity for mice. Gley and Girard's report[60b] on thioaniline gave further evidence that several compounds, in which the sulphur has different chemical functions, are able to arrest the evolution of streptococcal infection in mice. The pyridylsulphide[88] has a definite curative effect on intradermal streptococcal lesions in rabbits but it is more toxic than "Prontosil Solution." The pyridine compound,[81] although it has the benzene sulphonamide group, has a pyridine nucleus replacing the amine group. It is probably not converted into sulphanilamide in the body. It has a powerful antistreptococcus effect *in vivo*, is readily soluble and is practically free from toxicity for mice and rabbits.[81] The naphthalene compound of Buttle *et al.*[30] has a therapeutic index about the same as sulphanilic acid, and both of these are less active than sulphanilamide. I have included in the table a number of compounds referred to by Domagk,[45] "Serenium" to show its relationship to chrysoidine and Prontosil, and the pyridine azo compounds "Neotropin" and "Pyridium" since these have been used to combat infections particularly of the urinary tract.

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* In recent studies Levaditi and Vaisman used sulphoxide compounds (see Table I).

It would seem, even from this abbreviated review, that the substances therapeutically active against experimental infections with different bacteria are relatively numerous. Of these, sulphanilamide has been studied most completely and the importance of its molecular structure is evident. Sulphur in various functional states as sulphonamide, sulphonate, sulphone or sulphide* appears as a common constituent of this group of active substances and it is found as part of the radicals in many of the derivative compounds. The amine radical in the para position of the benzene ring seems to have some determining effect along with the sulphur containing radicals. Although the benzene ring is the basic constituent of almost all the effective compounds, Kolmer[88] believed the pyridyl nucleus offers greater possibilities for future study, particularly when it contains divalent sulphur in the molecule.

The solubility in water of these various preparations differs widely. Sulphanilamide is soluble 0.4 to 0.8% as the base (Hawking[74] gave 1.5 gm. in 100 ml. of water at 20° C.) and as the hydrochloride it is freely soluble in water; but this latter solution is acid and causes necrosis on subcutaneous injection.[30] It is of interest that Tréfouël,[155a] Fourneau[59] and Goissedet[62] used the hydrochloride. Buttle[30] found it too acid for use. Tréfouël (1937)[155b] used the amine, the sodium and the chloride preparations but found the latter too acid for toxicity tests, and Barlow[10] also reported that both the sodium and the hydrochloride were too irritant. Foulis and Barr[49] reported one patient in whom the drug (the base?) was ineffective until dilute hydrochloric acid was given preceding its ingestion, and Paton and Eaton[120] referred to 2 patients who were given hydrochloric acid to aid absorption, and they considered that these patients may therefore have received a greater effective dose. With very few exceptions it may be presumed that the base is the form in which sulphanilamide has been administered, but it may be converted into a more irritating form in the body. The sulphonanilide derivative is of low solubility. Disulphanilamide is also poorly soluble. Rosenthal[128] found it less effective against streptococci than sulphanilamide when given by mouth but it was much less toxic than the latter. "Uleron" is also only slightly soluble in water but is readily soluble in dilute alkalies.

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* In recent studies Levaditi and Vaisman used sulphoxide compounds (see Table I).

"Prontosil" is effective both as the base and as the hydrochloride,[45c] the latter is used in a 0.25% solution, but the base is often used in the tablets because the hydrochloride has a more bitter taste and is not well tolerated orally. To increase its absorption from the stomach hydrochloric acid is also given.[22, 29, 45a, 111] Jaeger[83] believed the base had a greater affinity for the skin than the chloride and also that it increased the clotting of blood on local application. It would appear that it is the hydrochloride which is usually referred to under the name "Prontosil."

"Prontosil Soluble" is, as the name implies, much more easily soluble, being used in 2.5 to 4% solutions and it has largely replaced the original "Prontosil." Both "Prontosils" have been frequently administered together, one by mouth, the other intramuscularly or intravenously, so that clinical statistics are confused as to which may be the better therapeutic product.

The formaldehyde sulphoxylate derivative is water-soluble, "Septazine" is only slightly soluble in water and is prepared in tablet form. The "Soluseptazine" is used in a 6% solution corresponding to a 2% solution of sulphanilamide. The sulphone compounds (diamino and dinitro)[32] are poorly soluble, the first 0.01%, the second is insoluble.

Evidence for the Curative Action. The therapeutic efficiency of these drugs has been established on the basis of animal experiments, chiefly mice. Intraperitoneal injections of mouse-virulent beta hemolytic streptococci has been the procedure in the great majority of the laboratory studies, and this is followed (occasionally preceded) by the particular drug which is given as a rule subcutaneously or *per os*. The evidence demanded was the death of the untreated controls within 24 to 48 hours and the prolonged survival or a marked delay in death of the treated animals.

Domagk[45a] using "Prontosil" indicated clearly that after the injection of about 10 fatal doses of the streptococcus (0.3 cc. of a 1:100,000 dilution of a 24-hour culture usually killed in 24 hours) the drug in doses one-tenth to one-fiftieth of the tolerated amount when it was given over a period of 3 to 5 days saved the life of a large majority of the mice. The most convincing evidence for its activity was obtained by a comparison of smears from the peritoneal exudate of the treated and untreated mice, the streptococci quickly disappearing from the former while in the latter they multiplied rapidly and caused a septicemic death. Backed by the clinical reports on a number of serious human streptococcal infections in which striking curative results had been obtained by the drug, this experimental work was repeated in France,[92] England,[36] and America.[94] It was soon discovered that a necessary condition for successful results in mice was the use of strains of hemolytic streptococci of a rather surprisingly high virulence.[36a, 92, 94, 116] Hemolytic streptococci from human infections are rarely of high virulence for mice, and usually a long series of passages was needed before satisfactory virulence was obtained. Further interesting observations were that it was rare to obtain a prolonged survival of all the animals treated however the drug was given; that living cocci could often be obtained from the blood or tissues of treated mice long after the untreated controls had died; and that those animals dying after long periods from streptococcal infections quite often failed to show the pathologic lesions characteristic of streptococcal deaths. Levaditi[92c] had mice dying of streptococcus septicemia 18 to 19 days after apparent cure, and Long and Bliss[94] had such delayed deaths after 39 days and even after 63 days and 128 days. The explanation of such results is particularly difficult if the drug is to be considered in the ordinary sense as a germicidal or even as an antiseptic agent.

The criteria of efficiency suggested by Buttle[30] were: (1) the number of lethal doses against which the drug will protect when given under optimal conditions; (2) the latest time after the infection when the drug is still able to save the animal. The minimal protective dose has also been used, and the prophylactic value of the drugs when given at various times preceding the infection. The latter seems to depend largely upon the rate of elimination of the drug from the body which depends more or less upon its solubility. It is indeed difficult to properly assess and compare the various drugs which are being used in these experiments, and if this is true under the comparatively rigid conditions of laboratory study how much more difficult it will be in the clinical evaluation. Whitby[161] gave a scheme for reporting these experimental results, under which the lethal dose must remain constant in both size and virulence. To obtain the average days of survival the number of mice surviving each day is multiplied by the number of days and the sum of these is divided by the number of mice used. Any particular drug in its action against any bacterium can thus be compared under the above conditions.

Beta hemolytic streptococci have been used in the majority of these experiments because their virulence can be kept reasonably constant, and the intraperitoneal route is the most convenient for obtaining comparable results. However, various sites have been used in these studies as will be seen later in this review. Berger[15] particularly employed the subcutaneous route to produce streptococcal abscesses in mice and gave "Prontosil Soluble" by mouth 5 hours later and repeatedly up to 5 days. He was thus able to prevent the general spread of the infection and the establishment of fatal metastases in a high percentage of his mice. He wondered whether all streptococci will be found to be as susceptible as the strain he used. It was at first believed that the drug "Prontosil" acted in a rather specific manner against streptococci as is indicated in the trade name "Streptozon," although the early clinical reports gave evidence that it was effective in a wider field,[91d] and Domagk[45a] himself had found it more or less active against staphylococci. These views were largely the result of the technical procedure in the experimental work and were soon radically modified. The beta hemolytic streptococcus has been shown to be particularly susceptible to all these drugs, and a number of workers considered that the streptococci of the Lancefield Group A, which includes all the primary and serious hemolytic streptococcal infections in man were almost exclusively susceptible. Long and Bliss[94c] found the A and B groups were affected, but in 4 patients with D group infections the drugs were valueless. It is true that most of the laboratory work and the dramatic clinical results in the human have been obtained with strains of this group. There has not been enough comparative work done, however, to make this suggestion tenable. Levaditi[92c] had good results using a hemolytic strain (M) from a horse with glanders. Tréfouël[155b] used a highly virulent animal strain (Pion) in his experiments on rabbits. Davesne and Brunschwick[41] believed they controlled a streptococcic epizoötic among newborn lambs by the use of "Prontosil" tablets, Stevens[149] in a letter reported the apparent cure of bovine mastitis by means of sulphanilamide, and Seastone,[143] using a strain of group "C" which gave an acutely fatal infection in animals, was able to prevent death with sulphanilamide. On the other hand, Colebrook and his colleagues,[36, 38] Long and Bliss[94] and others had no convincing evidence that the drugs were effective in man for other than Group A infections. It is clear that the evidence on either side is comparatively meagre, and until more detailed experiments are available it would seem wise to withhold final judgment. The character of the infection induced and the relative virulence of the organisms seem to be the important factors.

Other technical methods have also been used with hemolytic streptococci. Domagk[45a] treated rabbits successfully with experimental chronic infections in which the joint tissues were swollen and endocarditis was present. Tréfouël[155b] found the rabbit no better than the mouse for testing a series of chemical compounds. They used it particularly in studying the prophylactic or protective effect of sulphanilamide. Bürgers[29] carried out extensive experiments on 112 rabbits, 85 guinea-pigs and about 500 mice using intravenous, subcutaneous and intraperitoneal infections. Gay and Clark[58] showed sulphanilamide to be effective in experimental empyema in the rabbit. Kolmer[88] used skin and joint infections in rabbits in a study of eight compounds including the pyridyl sulphide mentioned above. Campbell[33] quoted Long as believing that "the rabbit is not a particularly good animal, because of metabolic peculiarities, on which to test sulfanilamide." The reason for this belief is not clear to the Reviewer, but until a fuller knowledge is available as to the mode of action of these drugs every factor must be seriously considered, particularly before applying the experimental results in animals to the explanation of the curative effects in man.

There is practically universal agreement that infections with alpha hemolytic streptococci (*Str. viridans*) are unaffected by these compounds; but even here the character of the lesion in subacute endocarditis, which is the infection usually considered, practically precludes the successful action of any agent, and I have not seen any report dealing with animal experiments using a highly virulent strain of *Str. viridans*.

Staphylococcus infections in rabbits were included in Domagk's original article.[45a] He had favorable results, particularly in acute spreading infections, but even in chronic infections curative effects were obtained although not as regularly as with streptococcus infections. It is of passing interest that the first article in the medical literature on the use of these chemicals reported a marked chemotherapeutic effect in a case of a generalized staphylococcal infection.[94d] The results in human infections will be discussed later. The difficulty in studying staphylococcus experimentally has been to find a strain of sufficient and constant virulence so that the untreated controls died with some regularity. It seemed to involve the same problem as was noted for streptococci with low virulence. Buttle[31] used a bovine strain and was successful in protecting mice by sulphanilamide against a thousand fatal doses. Hörlein[79b] reported that the three "Diseptal" compounds were strikingly more effective against staphylococcus in mice than sulphanilamide. Helmholz[76] found the urine of sulphanilamide treated patients to be bactericidal against staphylococcus.

In the case of the pneumococcus group the results have been most variable. Domagk[45] reported that "Prontosil" had some effect on Type III pneumococcus but not on Types I and II, and in 1936[45c] that sulphanilamide was more effective against pneumococci than was "Prontosil." Nitti[117] reported a direct inhibitory action of sulphanilamide *in vitro*. Buttle[32] found the diaminosulphone compound to be twenty times more effective than sulphanilamide in prolonging life in the mouse, but complete cure was uncertain. The explanation offered was the prolonged action of this drug due to its low solubility which is considered necessary for protection against pneumococcus in mice. Rosenthal (1934)[127a] showed that formaldehyde sulphoxylate was effective in curing mice infected with one particular strain of Type I pneumococcus but gave negative results with all other types and strains. In a later study[127b] he found sulphanilamide possessed a certain degree of chemotherapeutic activity against 7 strains of Types I, II and III infections in mice. He[127a, 129c] also found it bactericidal and bacteriostatic for pneumococcus *in vitro*, although no such effect was obtained with streptococci and other organisms. He and his associates[128] further showed that this drug was much more effective against pneumococci intraperitoneally in rats than in mice and rabbits. Branham and Rosenthal[23] had much better results when sulphanilamide was combined with specific serum therapy. Cooper *et al.*[40] using subcutaneous injections of about 10 lethal doses of a highly virulent Type III pneumococcus in the mouse was able to demonstrate a definite curative effect with sulphanilamide. They point out that because of the extreme susceptibility of the mouse to pneumococcus these results are of greater significance than the lethal doses would suggest. They[66a] later obtained good results with the same drug in rats infected intrabronchially with the same strain of organism suspended in mucin, and by this same technique further showed[66b] that Type I pneumococcus was controlled as effectively by the drug as by the specific serum. A combination of drug and serum gave somewhat better results. On the basis of these results they recommend its trial in man and include the suggestion that the occasional complicating hemolytic streptococcus infection would also be controlled. A more detailed study[39a] on some 64 rats infected as above with the strain of Type III pneumococcus showed that the effectiveness of the drug treatment varied inversely with the interval between infection and initial treatment, and with the size of the infecting dose. The treatment would appear to enable the surviving rats to overcome the associated toxemia which usually proved fatal in the controls, since the course and extent of the pneumonia was not appreciably affected. In a fifth report[39b] they used 2 strains of Type II pneumococcus and here also found the drug at least as effective as the specific antiserum, the combined drug and antiserum giving no better results. Kreidler[90] used rabbits infected with a Type I pneumococcus of high rabbit virulence intracutaneously and found that sulphanilamide if given early and in sufficient dose eliminated the pneumococcus from the blood, reduced the fever, cured the local lesion and favored recovery in most of the treated animals. Schmidt[135] used a Type XIV pneumococcus in mice intraäbdominally and was able to save all the mice if treatment with the drug was started within 4 hours of the time of infection even when large doses of organisms were used. Whitby[161] gave rather higher efficiency figures for his two diamino anilide compounds than for sulphanilamide using a Type I pneumococcus in mice. All of these results are most encouraging for an effective chemotherapy in pneumonia.

In the experimental study of Proom with meningococcus—first mentioned by Buttle[30]—the bacteria in 5% mucin were injected intraperitoneally in mice. Proom[123] showed that the protection afforded by sulphanilamide against Types I and II meningococcus is somewhat greater than that against hemolytic streptococci when the drug is given at once, either subcutaneously or *per os*. It prevented septicemia and death, and he had some evidence that the drug reached the cerebrospinal fluid when given by mouth. Rosenthal[128] confirmed Proom's findings, using the same technique, and compared the curative effects of a number of related compounds given subcutaneously. The disulphanilamide gave better results than sulphanilamide, "Septazine" gave only a fair percentage of cures, and "Prontosil" and "Prontosil Soluble" were not as effective. The formaldehyde sulphoxylate compound and the sulphonanilide were found inferior to the others. A further study,[23] using 20 strains of meningococci (Types I, II and III), demonstrated that sulphanilamide even in single doses 2 hours after the infection, especially when given subcutaneously, caused the survival of a large percentage of mice. A comparison with serum therapy gave irregular results, but when these were combined the results were definitely better and demonstrated a synergistic action rather than an additive one. Levaditi and Vaisman[92e] tested both "Prontosil" and sulphanilamide and found these drugs curative in the experimental infection induced by meningococci (Types A, B and C) in mucin. There was about the same irregularity as they had had in their experiments with streptococci. Whitby[161] used Proom's technique, confirmed his findings and reported that his sulphonanilide tartrate was just as effective as sulphanilamide, the average day survival being 4.2 for the former and 4.1 for the latter. "Septazine" and "Soluseptazine" had no appreciable effect. Brown[27] compared the relative value of sulphanilamide and a potent antiserum and found that 8 mg. of the drug was practically equal to 0.1 cc. of the serum. They also confirmed Branham and Rosenthal[23] that a combined therapy was more effective, and further noted that the percentage of positive blood cultures taken 8 hours after the infection was lower than when either serum or drug was used alone.

Because of technical difficulties there has been practically no experimental work with these drugs on the gonococcus,* but they have been widely used in the clinic because they are excreted by the kidney, and the favorable results with meningococcus offered some hope that they might be effective. For much the same reason the basic laboratory study with many other bacteria is relatively meager. Buttle[31] did preliminary determinations for members of the Salmonella group and other Gram-negative bacilli, obtaining a 75% survival in mice infected with *B. typhosus* and treated with sulphanilamide, although positive cultures could be obtained from blood or tissues a week or even a month later. Helmholz[76] found the urine after sulphanilamide to be bactericidal for most bacteria including *Proteus*, *B. coli*, *B. aërogenes* and others. Bürgers[29] found "Prontosil Soluble" had no effect against virulent Friedländer bacillus in mice nor against 7 strains of *B. abortus* in guinea pigs. Despite these results Berger and Schnetz[16] reported a favorable response to this drug in a patient with *Brucella abortus* infection. Nitti[117] had negative results with *B. typhi murium* in mice treated with sulphanilamide and the evidence from the spontaneous deaths in treated mice caused by a paratyphoid organism as mentioned by Levaditi[92] and by Long[94] is against these drugs having any useful effect on these Salmonella types. Bliss and Long[19b] used *Clostridium welchii* by intraperitoneal injections in mice previously given sulphanilamide by the same route and found that the drug protected the mice. The 3 untreated controls died in less than 7 hours from toxemia. Hörlein[79b] quoted Domagk as having had better results with the three "Diseptal" drugs than with sulphanilamide against gas gangrene in mice.

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* See recent work of Levaditi and Vaisman (note under Table I).

Campbell[33] was unable to obtain any effect with sulphanilamide in experimental syphilis in the rabbit. Buttle[31] had negative results with *Trypanosoma equiperdum* in mice as well as with avian malaria in canaries. Diaz de León,[43] however, had successful results with "Prontosil" in 15 cases of benign tertian malaria in man.

In the few virus diseases studied, Levaditi and Vaisman[92] found "Prontosil" without effect in experimental herpes (encephalitic strain) and lymphogranuloma inguinale. Kelson[84] also had negative results in experimental poliomyelitis in the monkey. The only successful result reported to date is that of Rosenthal, Wooley and Bauer[129] with "Prontosil" against the virus of lymphocytic choriomeningitis in mice. These same authors had negative results with other related compounds and were unable to obtain any effect against the virus of encephalitis (St. Louis type) or the virus of influenza.

Clinical Results. The publications reporting the clinical application of many of these new drugs to all manner of human diseases are so numerous that only mere references can be given to most of these. To avoid needless repetition dosage, methods of administration and other details will not be considered despite the fact that these are often of great importance. It may be said, however, that the intravenous route was used in the early days of "Prontosil" and "Prontosil Soluble," but the oral and subcutaneous routes are almost exclusively used today, and that other methods of administration have been employed only under special conditions. Since the chemical methods have been developed by Fuller,[56] and particularly by Marshall and his colleagues[98, 100] for determining the percentage content of sulphanilamide in the blood, urine, cerebrospinal fluid and other parts of the body, the most effective dosage can be very accurately determined. The mechanism of the excretion by the kidney[100c] is now better known and the distribution in the tissues according to their water content has been established.[100d]

Human Hemolytic Streptococcal Infections. *Erysipelas.* The evident difficulty in evaluating the results of any treatment of this disease is its frequent natural tendency to recover with or without treatment. It is, however, often impossible to predict how severe an attack may be in the early stages, and as prompt treatment is advisable evidence must depend largely on statistics. In the very young and in the older age groups erysipelas is apt to be more severe so that somewhat greater weight should be given to the results in such cases. In the following condensed summary only the briefest notes are possible.

"Prontosil" was used in the early cases reported in 1935 both as tablets and in the 0.25% solutions. Gmelin[61] treated 10 children and normal temperature resulted on the second to third day in 9, and in 1 on the fifth. Schreus[139] considered the drug a specific and had no resistant case in 18 months. Klee and Römer[86] had rapid recoveries even in the aged. Imhäuser[82] reported 4 cures. Scherber[133] in a long report compared the drug to "Omnadin" (a lipoid preparation containing the fermentation products of non-pathogenic bacteria acting as a non-specific cell stimulant), and showed a reduction in the average day of fever in favor of "Prontosil." Roth[130] had a good result in a necrotizing erysipelas of an entire leg as well as in 2 other severe cases. Lampert[91] reported rapid clinical results and in 2 cases, despite a septicemia with purulent metastases, had a prompt cure. In 1936, Kramer[89] reported 23 cases in which the fever disappeared in 2 to 3 days and the temperature and pulse became normal in an average of 4.3 days, under other forms of treatment this was 11.3 days. He had two failures, apparently due to too small amounts of the drug. Scheurer[134] had his most striking results in this disease and considered it a specific for the severe septic cases—other cases recover without treatment. Valerio[156] reported success in 3 very severe cases in infants. Tonndorf[153] treated 22 with no failures, the patients became fever-free in 2 days and often in 1. If the temperature did not fall promptly he looked for a complication, believing this of value in differential diagnosis. Meyer-Heine and Huguenin[110] treated 150 cases with only two failures. They were particularly impressed by their results in 8 infants. Bloch-Michel[20] used "Septazine" in 250 cases. In 170 cases of face erysipelas 9 died and 8 of these were over 70, but a very severe infection in a patient of 73 was cured. Frankl,[52] out of 40 patients treated, did not lose a case. He particularly stressed the disappearance under treatment of the immature white cells and considered a drop in the total white cell count a favorable prognostic sign. Meyer zu Hörste[111] gave statistics indicating the frequent high mortality from erysipelas in the newborn ranging from 27.3 to 80%. He used "Prontosil" base orally in his infant cases and accounted for at least one of his failures, if not two, by the failure of absorption due to lack of gastric acidity. When dilute hydrochloric acid was given with the base his patient promptly responded. Hartl[72] did not find "Prontosil" of any benefit in 21 cases, none of them septic, in that the cure was no more rapid than in the controls. Anghelescue *et al.*,[3] during 1934 and 1935, treated 631 cases and compared the results of ultra-violet light therapy in 20, antistreptococcus serum in 17 and "Prontosil" in 12. The average days in hospital in all was 15. Under light therapy this was reduced to 8, under serum to 12 to 14 and under "Prontosil" to 6. The responses to "Prontosil" therapy, as others have reported, were prompt. In 1937 they[4] reported particularly on the good results obtained in 6 cases with severe kidney complications and in which "Prontosil" not only cured the erysipelas but also improved the conditions in the kidney. Becker,[13] in a comparison of 50 cases treated by the drug with 50 under other treatments, reported a reduction in the duration and always the arrest in the spread of the infection in the treated cases, particularly when the drug was given orally. Peters and Havard[121] had striking results in 47 cases treated by "Septazine." The youngest patient was 4 months old and 3 were aged 70, 81 and 87. The temperature returned to normal as a rule in 24 (in 31) or 48 hours (in 12), only 1 having pyrexia up to the fifth day, and the spread was arrested within 24 hours in all cases.

Breen and Taylor[24] studied 46 cases in 35 of which sulphanilamide was used. Regression occurred in 48 hours in all but 2, one of these, a baby, responded soon after, and the other was an adult who later developed a lung abscess. They were particularly impressed by their remarkable results in the age group 50 to 65. Whitby[161] successfully treated 2 cases of erysipelas and 1 of cellulitis with "Septazine." Snodgrass and Anderson,[146] in a very carefully controlled study of 312 cases, treated 104 by ultra-violet light, 106 by "Prontosil" tablets (10 "Prontosil Soluble"), by a combined treatment in 54 and with antistreptococcus toxin in 48. Fifteen died and are not considered in the tables but the percentage of deaths (4.8) is much lower than in other years in the Glasgow area. In those receiving "Prontosil" the death rate was 2.5%, for the others 6.6. The tabulated results cannot be abbreviated but it may be noted that spread stopped in 2 days in 98% in the drug-treated cases and in 75% of the others; pyrexia over 3 days in 8% of the former and in 41% of the latter; toxemia persisted after 3 days in 21% of the "Prontosil" cases and in 39% of the others. In a symposium on Sulphanilamide Therapy[150] are reports of 42 cases in infants and young children in which 37 responded, 3 died and 2 were still in hospital. Among these Basman and Perley[12] had 3 cases of abscess formation in their 9 patients and they speculate, on the basis of the immunity in erysipelas being largely cellular, that the drug may abort the infection and on its withdrawal the bacteria still present may lead to abscess formation.

Despite the obvious difficulties in reaching a definite conclusion the evidence seems incontrovertible that this group of drugs has a remarkable curative effect on erysipelas at all ages and in its varying degrees of severity.

Scarlet Fever. It is of interest that here the results are apparently much less satisfactory, although it should be mentioned that comparatively few reports have been published. Peters and Havard[121] gave their results in 150 cases treated with "Septazine" as compared with 150 controls (56 of which had been given antitoxin). The complications were 35% in the former as against 56% in the latter. They suggested for future trial a combination of antitoxic and drug therapy.

Miscellaneous Oral Infections. Various types of angina including septic sore throat, tonsillitis and various complications such as cervical cellulitis, and other throat infections predominantly caused by hemolytic streptococci, have been treated by these drugs with, as a rule, very encouraging results. Klee and Römer[86] used "Prontosil" in a series of severe septic cases and they have had no fatality in this serious type of case in the 2-year period during which this drug was available. They gave the histories of 4 typical cases. Schranz,[138] after 2 years' experience with the drug, recommended it in cases of angina both intravenously and as a gargle, using the dissolved tablets. Recknagel[125] gave the history of a case of acute sore throat with arthritic pains which responded promptly. Roth[130] reported the successful treatment of a case of streptococcus septicemia following a sore throat. Tixier and Eck[152] refer to a gangrenous angina cured by "Prontosil." Kramer[89] recommended it for septic throats. Scheurer[134] had an excellent result in a case of purulent angina. Domagk[45c] considered the drug valuable when given by mouth in all types of oral infections because of its being locally absorbed. Jaeger[83] used a concentrated watery solution of "Prontosil Soluble" for local application in angina cases. Long and Bliss[94b] cured 14 cases of tonsillitis and 5 peritonsillar infections with sulphanilamide and its derivatives but lost 2 cases of Ludwig's angina, these patients dying within 20 and 35 hours after beginning the treatment. Two cases of Ludwig's angina which recovered under "Prontosil" treatment are briefly reported by Palmer[119] and by Lyth.[96] Massell[102] studied the effect of sulphanilamide on hemolytic streptococcus infections in the respiratory tract in 6 cases of rheumatic fever and compared these with 6 similar cases given "Aspirin." The results were identical in that recrudescence occurred in 2, adenitis in 1 and death in 1 of each group. A very severe tonsillitis with high fever and inability to swallow which responded rapidly to intramuscular "Prontosil" is reported by Salama.[131] Peters and Havard[121] reported success with "Septazine" in 15 cases of streptococcus tonsillitis, at first thought to be diphtheria, after 48 hours of treatment and in a case of faucial cellulitis from a tooth after 72 hours. Whitby[161] had seven successes and two failures in treating tonsillitis with "Septazine." Kenny[85] mentioned 2 cases as having developed tonsillitis while under treatment for bacteriuria with sulphanilamide. Macnaughton[97] had 2 severe cases of tonsillitis which were cured by intramuscular "Prontosil Soluble." McIntosh[103] reported rather irregular results. Hageman[69a] had excellent immediate results with sulphanilamide in 7 cases of tonsillitis, but hemolytic streptococci persisted in the throat for as long as 5 weeks. Basman and Perley[12] found all of 15 cases of tonsillitis and similar infections did well, but in 9 the clinical improvement was marked under sulphanilamide. Brennemann[25] had favorable results in acute hemolytic streptococcal sore throats in 6 cases: cultures became negative but, a week after the drug was stopped, these again were positive. Smith[145] reported an epidemic of acute tonsillitis in 45 persons from 1 to 45 years old in which 39 were treated. Sulphanilamide was used in 22 (also "Prontosil Soluble" in 4) and "Septazine" in the other 17. Hemolytic streptococcus was cultured from 31, and from 8 less acutely ill *Str. viridans*. The striking effects were in the hemolytic streptococcus cases in that the acute illness was over within 48 hours. There were 5 relapses 2 to 4 weeks later and these again gave a prompt response to the drug. Throat cultures were positive up to 4 weeks after recovery which suggested to him that this treatment may increase the carrier rate. Thirty patients were given the drug prophylactically with apparently good results. Gallagher[57] also had an epidemic of hemolytic streptococcal pharyngitis and 33 patients received treatment with sulphanilamide with the result that the length of time the throat cultures were positive was significantly reduced, the results seemingly being dependent on the size of the dose and the stage of the infection when it is given.

Otitis media and *mastoid infections* have been treated with sulphanilamide and the results have, as a rule, been excellent with an occasional dramatic cure (Hageman,[69a] Basman and Perley[12]), and sometimes the cases cleared up without a suggested operation being necessary. Hemolytic streptococcal infections did particularly well.

Hemolytic streptococcus meningitis is an infection with such a high death rate that the curative results with these drugs is the most convincing evidence for the high value of this therapy in severe human infection. Gray,[64] in 1935, was able to collect from the literature since 1901 only 66 recoveries. Trachsler *et al.*[154] have added 22 from the literature and one of their own, if we accept 9 in which the hemolytic character of the streptococci is not given (they also tabulate 7 cases of non-hemolytic meningitis), so that the reports from 1901 to 1937 total 89 recoveries out of we know not how many hundreds of fatal cases in which sulphanilamide and its derivatives were not used. The following is a list of cases successfully treated with these drugs, the number of cures when known follows the reference. Caussé[154] (1) the first case reported in February, 1936; Arnold[7] (1) and has since had 4 others[94d] (4), Lucas[95] (1), Vitenson and Konstam[158] (1), Schwentker[141] (3), Anderson[2] (1), Frazer[53] (1), Draeseke and Raynor[46] (1), Weinberg[160] (2), Martin and Delaunay[101] (1), Hageman[69a] (1), Basman and Perley[12] (1), Trachsler[154] (4), Millet[112a] (1), Long and Bliss[94d] (2), they also saw in consultation 9 other patients of whom 8 recovered (8) and Colebrook and Purdie[37] referred to reports by Rouget and Vaidie, Le Mee and Salmon and Neal *et al.* (3). There have been in addition 6 cases of hemolytic streptococcal meningitis in Toronto cured by sulphanilamide. Five of these are reported by Silverthorne and Brown.[144] Thus we have a record of at least 43 recoveries in less than 2 years or practically half the previous record covering over 35 years.

Puerperal infections with hemolytic streptococci are among the most serious of human diseases as well as most variable in their outcome. The difficulty in evaluating statistics has been recognized by all, and in case of successful therapy the favorable results may be due to other factors such as the presence of streptococci of reduced virulence. Virulence as Gibberd,[59] Colebrook[36,38] and others have emphasized is chiefly determined by the evidence of invasion of the organisms into the tissues. The striking results obtained by the use of these new drugs are well represented in puerperal fever and infected abortion cases, especially in those due to beta hemolytic streptococci.

Klee and Römer[86] failed to prevent a fatal outcome in a late case of septic abortion with marked involvement of the perimetrium. Anselm[5] cured 2 cases of sepsis after miscarriage, in one of which there was a pyosalpinx and a Douglas abscess. In 13 other cases of puerperal fever treatment was started at once on admittance with excellent results. He gave "Prontosil" intravenously in the severe cases. Imhäuser[82] was enthusiastic over "Prontosil" therapy for such cases, and gave the histories of 2 puerperal fever cases (one was due to hemolytic streptococcus) and of 4 cases of febrile abortion. Schranz,[138] after a 2-year survey of the use of this treatment, gave as examples of its curative effect detailed accounts of a case of puerperal sepsis and one of post-abortion sepsis. Fuge[55] in 18 months' experience with "Prontosil" did not lose a case from streptococcus sepsis—his two failures were: in one, death the day after removal of a dead fetus and with streptococcus and staphylococcus metastases already present; in the other, a pure staphylococcus sepsis with widespread metastases. He defined sepsis as the condition when "an infected focus has been formed in the body from which pathogenic bacteria pass out constantly or periodically into the circulation in such a way that subjective or objective disease phenomena are produced by this invasion." He treated 120 women, including 14 cases of sepsis, and obtained excellent results. He emphasized the need of general treatment which by itself has often resulted in cure. Tixier and Eck[152] reported 1 successfully treated puerperal fever case. Vermelin and Hartemann[157] used the drug only in serious cases. They had some difficulty with the available brands of "Prontosil" and give details of 2 cases, 1 having a severe chill after the second injection and in 1 the drug may have caused the death. Sommer[147] also reported a fatal result after the intravenous injection of a solution made up from a new tablet preparation.

The best sustained studies of this therapy in puerperal fever and related infections have been those of Colebrook and his colleagues, and a review cannot do justice to the careful and unprejudiced analyses they have made of their results. Their first trial[36a] of "Prontosil" was made after a very full study of the effects of the drug in experiments on animals, and because of the high virulence of the streptococci demanded under these conditions they were not very hopeful that it would be successful in the human. They treated 38 cases and reduced the death rate to 8% from one of 26.3 in the preceding 38 cases and from an average of 22% over a 4-year period. They noted that the streptococci could be cultured from the discharges of treated cases just as often and for just as long as had been found in their previous cases. In a second report[36b] 26 further cases with no deaths are considered, but the statistical study of the different types of infection in the then total of 64 cases cannot be profitably reviewed. They believed that in at least 20 or 30 of these the course of the infection had been profoundly modified by the drug. The most striking results seemed to be in the fall in the death rate (4.7), especially from peritonitis, failure of the spread of the infection to the cellular surrounding tissues, the rapid drop in the temperature and the cure of 9 out of 12 cases with positive blood cultures. Their last report[37] covered their results with sulphanilamide in 100 cases with 8 deaths (a note refers to 15 additional successful cases giving a death rate for hemolytic streptococcal infections of 7%). In the final total of 199 cases of hemolytic streptococcal infections treated by either drug the death rate was 5.5 as compared with 22.8 in the 5 previous years. They believed "Prontosil" is slightly better than sulphanilamide. Another excellent report covering some of these same cases is that by Gibberd,[59] who showed a death rate of 4.5 for the 157 cases treated between January, 1936, and March, 1937. This report should be read in its entirety for the detailed analysis of this valuable material.

In the interval between these reports, Ley,[93] who had used "Prontosil" given by various routes for some 2 years, gave his results for

37 cases treated therapeutically with four failures (given in detail) and for 42 cases in which it was used prophylactically before operation or other interferences usually associated with a later pyrexia. Of these latter cases, 35 did not develop fever and only 1 died. He was very enthusiastic but emphasized that treatment should be started before 48 hours after a rise in temperature to obtain the best results. Long and Bliss[94a] had success in a case of infection after abortion with a pelvic peritonitis. Foulis and Barr[49] used sulphanilamide in 22 severe septic cases (11 septicemia, 4 peritonitis and 7 others—all hemolytic streptococci) with a rapid and striking fall in temperature and general improvement. In 4, "Prontosil Soluble" was also given. One patient died, making a death rate, from a total of 70 septic cases in hospital in a 3-month period, of 1.4%. Peters and Havard[121] treated a case of puerperal fever and infiltration of the broad ligament by "Septazine" with a prompt curative result.

Hemolytic Streptococcus Bacteremia Other Than Puerperal. There are a number of reported cases which merit reference. Roth's case,[130] already mentioned, followed an oral infection and was cured under "Prontosil." Lampert[91] had 2 successful cases after erysipelas. Long and Bliss[94a] treated 3, 1 of these died 7 hours after treatment was commenced, had been ill for several days and was practically moribund. The other 2 recovered. Robinson[126] was successful in treating a very severe case with "Prontosil" and although antiserum was also given, the cure is most probably due to the drug. Whitby[161] treated 5 cases with "Septazine" and had one failure. McIntosh[103] had 2 successful cases treated with sulphanilamide. Mitchell and Trachsler[113] treated 3 children, 1 died and 2 recovered, but for only 1 of these was the drug given credit. Carey[34] was successful in 5 cases and Basman and Perley[12] in 1. Brennemann[25] reported a case in a child with an infected hip and hemolytic streptococci grown both from this site and from the blood. The child was recovering at the time of the report. Maenaughton[97] treated with success by "Prontosil" a very severe bacteremia from an infected ear with repeated positive blood cultures.

Hemolytic streptococcus peritonitis cases other than puerperal have been occasionally treated. Long and Bliss[94a] failed in a 4-month-old infant, as did Basman and Perley[12] in a baby; and Bernstein[17] was unsuccessful in a boy of 6 who also had a bacteremia. Brennemann[25] cured a boy of 9 and McIntosh[103] reported 3 cases of "primary" peritonitis in infants and had in 2 a favorable and in 1 a questionable result under sulphanilamide treatment.

A variety of other hemolytic streptococcal infections have responded to this chemotherapy. Gmelin[61] gave a short note on his excellent results in 2 cases of empyema after giving "Prontosil" by mouth. Schranz[138] injected "Prontosil" about the site of operation as a prophylactic. Domagk[45c] treated a severe infection in his own daughter. After a needle which had entered her hand was removed a phlegmonous inflammation spread to her arm. When repeated incisions failed to stop the spreading infection she was given a series of treatments with "Prontosil" by mouth and rectum, and a complete cure was obtained. Jaeger[83] used "Prontosil" chiefly as a saturated solution in equal parts of alcohol and acetone as a local treatment in a great variety of conditions, such as cuts, street wounds, and to replace iodine in surgery. Long and Bliss[94b] had success in 2 cases of streptococcus osteomyelitis. Peters and Havard[121] were able to stop a hemolytic streptococcal pleurisy following an influenzal pneumonia after only two aspirations by means of "Septazine." Brown[26] reported the marked benefit he obtained by the use of "Prontosil" given intrapleurally in 2 patients with streptococcal empyema after influenza and who were in extremely poor condition. Bensley and Ross,[14] in a special study on methemoglobinemia in sulphanilamide therapy referred to a case of hemolytic streptococcal pneumonia, cyanotic on admission, and who developed methemoglobinemia so that an estimated 22% of the total hemoglobin was involved. In this case the anoxemia was aggravated by this condition. McIntosh[103] had a favorable result in an infant with a streptococcal pneumonia. Hageman[69a] listed 5 cases in their pediatric service in 3 of whom empyema was present before treatment, 2 of these required thoracotomy and all recovered. Basman and Perley[12] had an empyema in a baby cured by thoracotomy and the drug, and a 1-year-old boy, with an empyema 10 days after a pneumonia before admission, died in spite of the drug. Smith[145] reported 2 cases of acute septic arthritis of the hip, both gravely ill, which recovered under treatment with these drugs. Long and Bliss[94b] listed 3 cases of traumatic orbital cellulitis with a hemolytic streptococcus infection, all recovered. They had also 3 recoveries in streptococcus urinary cystitis. Colebrook and Purdie[37] mention an unreported case of extensive suppuration in the cellular and bony tissues of the pelvis, not of puerperal origin, in which a dramatic result followed sulphanilamide therapy. A particularly interesting case is the one reported by Purdie and Fry[124] of a chronic streptococcal infection with many abscesses and a history going back almost 3 years to a puerperal infection. The streptococcus found at the time of sulphanilamide treatment was the same serologic type as that grown from the primary infection. After 19 days' treatment in hospital with the drug by mouth and local irrigation of the abscesses and use of sulphanilamide powder, the discharge lessened, the wounds were healing, the cultures became sterile 4 days after and a complete cure was effected. This, then, is a short account of the situation in respect to the treatment of hemolytic streptococcal infections in man and it must be looked upon as indicating a new and highly encouraging advance.

Staphylococcal infections are different in the type of lesion produced, the relatively low invasive character of the organism and in many other ways. The experimental work with these chemicals preceding their application to human infections was, as outlined above, rather meagre and unsatisfactory. Nevertheless the drugs have been given many trials and at times with surprisingly good results. The first reference to "Streptozon" ("Prontosil") in the literature[94d] reported a marked chemotherapeutic effect in a case of generalized staphylococcal infection. Schranz[138] treated with success an upper lip furuncle which contained both streptococci and staphylococci with "Prontosil" and also a case of the same kind with only staphylococcus as well as another pure staphylococcal skull wound. Anselm,[5] having had a prompt response and a rapid cure in a mixed infection of streptococcus and staphylococcus in a patient with high fever after an abortion at the third month, treated 2 puerperal pyretic patients with a pure staphylococcal parametric infection with equally good results. Schreus[139] found "Prontosil" although not as selective as in streptococcal infections had nevertheless a definite effect. He treated a young child covered with staphylococcal abscesses over most of the body, a positive blood culture, and so seriously ill that death was expected daily. "Prontosil" was given by mouth twice a day, the abscesses softened, the temperature fell and the patient recovered. However, in cases of furunculosis his results were not satisfactory. Imhäuser[82] had failures in 2 septic cases. In one there were intracranial foci and death from meningitis. In the other, despite care and prolonged treatment with "Prontosil," death followed with leukopenia, in which no leukocyte reaction could be induced even by a turpentine injection. (Was this possibly a case of leukopenia from the drug?) Tonndorf[153] used "Prontosil" in phlegmons, furunculosis and similar infections and believed it did good, but found it impossible to draw definite conclusions. Meyer zu Hörst[111] considered the drug shortened the duration of furunculosis in infants. Jaeger[83] used the preparation referred to above locally in cases with furuncles, carbuncles and a variety of similar conditions and claimed to have had excellent results. Long and Bliss[94a] treated with sulphanilamide a resistant case of impetigo from which hemolytic streptococcus and staphylococcus were cultured with the disappearance of the streptococcus within 4 days and a slow clearing of the lesions. Walther[159] mentioned 2 patients with severe urosepsis, one with *S. aureus* alone and a positive blood culture, the other with this organism and *E. coli* that responded to a combined therapy of "Prontosil" intramuscularly and sulphanilamide by mouth. Basman and Perley[12] lost 2 cases with staphylococcemia, and in an osteomyelitis case with a double infection which recovered noted that the streptococcus disappeared first, and believed the drug may have helped. Colebrook and Purdie[37] had 3 puerperal staphylococcal infections of which 2 were cured.

Meningococcus meningitis is obviously an infection which might be expected to respond to this new therapy following the experimental work and the remarkable results in the streptococcus cases. Proom[123] believed the bacteria are carried to the meninges by the blood. Schwentker, Gelman and Long[142] treated with sulphanilamide 10 cases of meningococcus meningitis and 1 of meningococcemia. The drug was given subcutaneously and intraspinally and the cerebrospinal fluid became sterile in 3 days or less. In the 1 fatal case, the desperately ill patient had had a sterile fluid for 3 days and the cell count had been reduced to 158 when he died from a pneumonia on the fifth day. McIntosh[103] reported 2 cases of meningitis with bacteremia, which treated with specific antiserum and sulphanilamide, were both cured. Mitchell and Trachsler[113] had 3 recoveries following a combined therapy of antiserum, antitoxin and the drug intraspinally and by mouth. In one of these the spinal fluid had given cultures for 10 days but became negative the day after the first intraspinal injection of the drug. Bernstein[17] reported 2 recoveries, in 1 receiving only a transfusion of blood the recovery was slow, in the other both antiserum and drug were given and recovery was somewhat more rapid. Carey[34] treated 5 cases with the drug alone given by various routes. The blood cultures were positive in the 3 in which the blood was cultured. All recovered without sequelae. Basman and Perley[12] report 2 recoveries, in 1 a single injection of 15 cc. antiserum was given in addition to the drug therapy. Brennemann[22] treated 1 case with 3 large doses of antitoxin, "Prontosil Soluble" and sulphanilamide, the case recovered but the value of the drugs was of course uncertain. Schwentker, in the discussion of a paper by Bliss and Long,[19b] referred to having used sulphanilamide in 52 cases of meningococcus meningitis with a mortality of 15% as compared to a 30% mortality among patients treated with antiserum in the same hospital during the same epidemic. The evidence from the above results and the experimental work would suggest that a combined sulphanilamide-antiserum therapy is perhaps the best treatment.

Gonococcus infections have been much more widely treated with sulphanilamide and its derivatives than the reports in the literature would indicate. This is suggested by the relatively high percentage of cases of gonorrhea mentioned in reports in which secondary effects, particularly in the skin, are being considered.

Domagk[45a,b] compared the chemical structure of "Prontosil" and a number of chrysoidine compounds, which under trade names have long been recommended for urinary tract infections and for gonorrhea. The new drug was therefore given a trial by many. Schreus[139] did so, but found it unsatisfactory, although he obtained a definite action on the fever and local lesions, especially in acute cases. I have not seen his promised report covering his later experience. Becker[13] recorded a complete failure for "Prontosil" therapy in gonorrhea. Dees and Colston[42] in a preliminary report gave their results with an exclusive sulphanilamide therapy in 19 cases. The active discharge rapidly disappeared after the following days (cases in parentheses): 1 (3), 2 (7), 3 (2), 7 (2)—in the others more irregularly. The smears became negative in most in the first week after treatment. In 5 or 6 the response was slower and in 3 or 4 there was little if any benefit. They also had good results in chronic prostatitis. They found that the drug checked the spread and prevented complications, but they fully realized the need for a longer and more extensive experience. In 28 additional cases (making a total of 47) they had equally good results; there was never a progression of the infection even in the cases showing no response to treatment. Grütz[68] carried out clinical tests, with a number of preparations not on the market but supplied from Domagk and his associated chemists, in which it was demanded that the drug given *per os* be readily absorbed and reach the various sites where the gonococcus grows as an epithelial parasite, particularly in the lumina of the urogenital glands, that local and other treatment be stopped during the tests and that the results must be evident in a few days. Under these conditions "Prontosil" showed little activity, sulphanilamide had definite effects in reducing the numbers and causing the disappearance of the gonococci, but this was not constant and the disease sometimes progressed so that new preparations were tried. Three of these D.B.90 (Uleron or Diseptal A), D.B.87 (Diseptal B), and D.B.32 (disulphanilamide or Diseptal C) were found to be superior to sulphanilamide. He reported his results in 36 cases of both sexes with acute and chronic disease showing direct curative effects in 24 and failures in 12 (of which 9 were complete). Some of his failures he thought might have been due to poor absorption resulting from alkaline changes in the gastro-intestinal tract. There were a number of secondary reactions from the drugs but none of these were serious. He considered the drug Diseptal B (D.B.87) the best, so that it is not clear why Diseptal A (D.B. 90) was chosen for the later more extensive study. Hageman,[69a] using sulphanilamide, reported obtaining negative smears after 36 hours in a case of ophthalmia, and one good response out of three in vaginitis cases. Ballenger[8] had better results in a number of resistant cases by a combination of thermotherapy and sulphanilamide and strongly advocated its use in these resistant types of infection. Walther[159] referred to having treated 8 cases with sulphanilamide and regarded it as a useful drug. Felke[47] used D.B.90 (Diseptal A) and in a note gave it the name "Uliron." The most interesting point in his report is the stress he laid on the necessity of the tissue reactions in determining the final and complete cure of gonorrhea whatever the treatment may be. He considered that at the fifth to sixth week in untreated gonorrhea a stage is reached when a few bladder washings (Janet's original technique) will bring about a cure. He had some 50 case histories supporting this view, and even an epididymitis was believed to bring about more rapidly this "preparation for cure." The situation is different in the female in that involvement of the adnexa interfered with cure. He had given up the local use of silver preparations in all acute cases, at least in male patients. Reference is made to the use of "Prontosil" by many clinicians, but, with the exception of Linser, the only result was a rapid clearing of the second urine specimen but not a permanent cure. He found in 50 cases treated with "D.B.90" ("Uleron") that he could not abort acute cases in that, although the signs and symptoms disappeared in 1 to 3 days, the gonococci remained, because time is needed for the biologic defense. In ambulatory cases he allowed 2 weeks to elapse before giving the drug, and had even better responses in older infections and in those with epididymitis. His clinic treats mostly male cases, but he said that females were rapidly cured if the tubes are not involved. He found the blood of treated cases did not inhibit the gonococcus.

Uleron (the Winthrop Chemical Company's name for this drug) (also known as Diseptal A) is not being marketed in North America, but has been made available in a number of medical centers for clinical trial. The therapeutic results have been remarkably good, but because of certain undesirable effects (which have not been reported in the literature and which were unpredictable from the favorable biologic findings) the drug has been withdrawn for further laboratory investigation. Orr[118] treated 104 male and 30 female cases of gonorrhea, mostly ambulatory, with sulphanilamide given by mouth and used no local treatment with a resulting cure in 87.3%. Among the 17 cases in which the treatment failed, none showed any beneficial effect at any time. Keefer, in discussing a paper by Bliss and Long,[195] said that when sulphanilamide is added to whole blood or plasma these become bactericidal for the gonococcus, as was also the case with the blood of treated cases. He reported success in sterilizing the synovial fluid after giving the drug by mouth in several patients with gonococcal arthritis. Cokkins[25] published his early results after treating 250 cases with sulphanilamide *per os*. He considered it an effective remedy for gonorrhea and most of its complications, and that all the clinical cures could be made permanent if the drug is continued for 2 to 3 weeks. It must also be given in potentially toxic doses. Chronic urethritis and prostatitis cleared up at least as rapidly as did the acute infections, but a small group completely failed to respond.

Pneumococcus infections have been treated in only a few cases. Heintzelman[75] had 19 cases of Type III pneumonia, 9 of whom received sulphanilamide and 10 did not. Seven of the treated recovered and only 2 of the untreated. From 33 untreated cases in Pittsburgh only 9 recovered, giving a 75% death rate, as compared with 22% under the drug therapy. Basman and Perley[12] reported a Type V pneumococcus meningitis in a child which recovered under this therapy—the first proved case of pneumococcus meningitis in their hospital which was not fatal. They also had a second case of Type III infection in which the drug failed and another which died 15 hours after admittance. A Type V as well as an untyped mastoid case and a Type III brain abscess case all died. Of 2 cases of Type I empyema 1 recovered and 1 died, while a Type II pneumococcemia recovered. Millet[112b] had a successful result in a Type III pneumonia patient. Keith, in Toronto, had a case (not yet reported) of Type III pneumococcus meningitis which recovered promptly under sulphanilamide therapy. There are other scattered references to the use of these drugs in middle ear and other infections but the results were rather irregular.

Kidney Infections. These drugs have been and are being rather widely used in kidney infections with *E. coli*, and other bacteria. Klee and Römer[86] did not find "Prontosil" of any value in clearing up the bacteriuria in an epidemic of typhoid fever. Imhäuser[82] gave details of 4 cases of *B. coli* pyelocystitis which he cured by "Prontosil" therapy. Holzmann[78] warned that pyuria in children tends to show defervescence and improvement at 7-day periods, a fact which he held as important in prognosis and in preventing therapeutic hyper-enthusiasm. Huber[80] quoted Temming as the first to use "Prontosil" in 3 cases of pyuria in children, and Pernice, who had good results in 18 coli-pyuria cases in the young. He tabulated his own therapeutic results in 14 young females showing the clearing of the urine, the drop in the fever and the favorable outcome in both acute and more chronic cases. Hofmann[77] quoted Unshelm as having had a large measure of success in similar types of cases. Long and Bliss[94c] referred to the slow excretion of sulphanilamide through the damaged kidney as a danger in such therapy. Borst[22] treated 13 cases of coli-pyelocystitis with "Prontosil," and in 5, toxic symptoms were produced, and in 1 of these a fatal agranulocytosis suddenly developed. Kenny[85] reported 46 cases of *E. coli* infections of the urinary tract in all of which there were clinical symptoms which disappeared under sulphanilamide treatment, and the urine became sterile usually in a few days. The urine of the treated cases shown to contain sulphanilamide both free and combined was found to be bactericidal to a large number of bacteria isolated from the cases. The different strains varied in their sensitivity to the drug but the patients having resistant strains responded to treatment just as well as those with sensitive strains. Mitchell and Trachsler[113] had a case of coli-pyelitis which was improved by the treatment, Hageman[69a] a pyuria which cleared completely in 48 hours, and Basman and Perley[12] had a similar result but in another the child was sensitive to the drug. Helmholz[76] showed that sulphanilamide causes the excretion of an alkaline urine which is strongly bactericidal for most of the organisms found in urinary tract infections—the chief exception being *Str. fecalis*—and that this drug therapy is successful even in cases of urinary insufficiency.

Mellon and Shinn[107] were able to demonstrate bacteriostatic effects in urine if urine is used in the media and the diluent in place of broth. Sulphanilamide 1:10,000, a concentration often found *in vivo*, was particularly effective. Walther[159] considered that sulphanilamide will occupy an important place among the urinary antiseptics. Barer,[9] in a case of typhoid bacilluria unaffected by hexamine and ammonium mandelate, found the bacilli disappeared permanently from the urine under sulphanilamide treatment.

Miscellaneous Diseases.—There are many reports published on the use of these drugs in all manner of diseases. In acute rheumatism, Veil and Recknagel[125] reported a drop in temperature and in the sedimentation rate, McQuarrie[105] had a case which greatly improved under sulphanilamide, and there are other references in which the results are very uncertain or fully negative. Bingold[18] reported an apparent cure in a case having the Ebstein type of remittent fever, lymphopenia and eosinophilia and enlarged lymph nodes which, however, was not proved but was suspected as being Hodgkin's disease. Skin diseases of various kinds have seemingly responded. Jaeger[83] had a good result in a case of lupus erythematosis, the progress in a case of psoriasis was stopped, and "Prontosil" in alcohol and acetone was particularly effective in weeping eczema and in dermatomycosis. Bohlman[21] successfully treated 3 cases of gas gangrene with sulphanilamide and a combined gas bacillus antitoxin. In one of these cases the result was truly dramatic. He suggested that part of the effect may have been due to the prevention of the symbiotic growth of the streptococci.

Little need be said in reference to specificity after reading this review. The problem arises as to whether the kind of tissue reaction, dependent in many cases on the virulence and type of infecting organism, favors the action of these drugs or whether it is a peculiar bacteriostatic effect with variable results affecting in different ways the invasive and pathogenic characters of the bacteria. Hofmann[77] showed that "Prontosil" reaches a sterile turpentine abscess during the active stage, but after the abscess has ceased to progress the dye is no longer found in the pus. This may be also true for the other drugs.

Pharmacology and Secondary Reactions. However effective in therapy this group of drugs may be, and their value is indeed no longer questioned, yet they are all more or less toxic to animals and man. Secondary reactions, some trivial, some serious, are extremely common when they are given to patients ill with various diseases. Weese and Hecht are quoted by Domagk,[45] Hörlein[79a] and others as having shown that "Prontosil" is a very indifferent drug in animals. It had in rather large doses little demonstrable effect on the blood or the functions of the various organs, but with clinical experience and more extensive studies in animals and man the belief that this and similar drugs are innocuous has been rudely shaken.

Evidence for the toxic effect accumulated. Domagk[45a] observed that 0.5 gm. per kilo of "Prontosil" was well tolerated by mice and dogs *per os*, but that the cat only tolerated 0.2 gm. per kilo. Tréfouël[155] found sulphanilamide less toxic than "Prontosil" in animals. Bloch-Michel[19] confirmed this and also noted the lower toxicity of "Septazine." Buttle[30] confirmed Tréfouël's findings. In a comparative study of diaminodiphenyl sulphone, Buttle[32] found this drug 10 times more toxic than sulphanilamide in single doses and 20 times in daily doses in infected mice, but not for normal rabbits or monkeys. It was, however, curative in mice in a dose 100 times less. Proom,[123] in his experiments, used sulphanilamide suspensions subcutaneously and orally, but not intraperitoneally because of its toxicity by the latter route. Whitby[161] reported on the relative toxicity of "Prontosil Soluble," sulphanilamide, "Septazine," "Soluseptazine" and other compounds, finding "Septazine" relatively non-toxic. Halpern and Mayer[71] found "Prontosil" and sulphanilamide slightly but not negligibly toxic, and that they affected the nervous system in the order given. "Septazine" was definitely less toxic. The therapeutic coefficients they gave as $\frac{1}{10}$ for sulphanilamide, $\frac{1}{4}$ for "Prontosil" and $\frac{1}{40}$ for "Septazine" in the mouse and other animals. Hawking,[74] in a pharmacologic study of sulphanilamide base, reported that in acute poisoning the central nervous system was involved but the other organs showed no evident change. In a 1:1000 solution it had no effect on the rabbit intestine or guinea pig uterus *in vitro*, and a 1.5% solution did not change the blood pressure in the cat and dog. Large doses in the peritoneal cavity had practically no irritating effect. The toxicity tests by Rosenthal[128] on sulphanilamide and other compounds have already been mentioned. Hageman[69b] studied the pathological lesions in mice produced by 50 mg. of "Prontosil Soluble" or 20 mg. of sulphanilamide given parenterally each day for 2 weeks. There were no reactions noted to the first drug, but with the latter severe nervous symptoms occurred. The finding of hemosiderin in the spleen of the sulphanilamide-treated animals suggested increased blood destruction. Barlow[10] found the M.L.D. for "Prontosil Soluble" and disulphanilamide *per os* was over 40 gm. per kilo in mice, that for sulphanilamide given in 50% acacia was 6.25 gm. By the subcutaneous route the M.L.D. for "Prontosil Soluble" was 6 to 8 gm. and for sulphanilamide 2.75 to 4 gm. per kilo.

Toxicity in Man. In this brief consideration of toxicity in animals it may be noted that many factors influence the results, and that the animal species differ in their reactions. It is, therefore, only in man and almost exclusively when he is suffering from some infection that useful facts about the actual toxicity of these drugs in human therapy can be obtained. The literature on this phase of the subject covers the vast majority of all the reports. I will attempt very briefly to group these under a number of headings.

Blood. Many have realized the potential danger suggested by the presence of the benzene nucleus in most of these drugs. Cyanosis is one of the most common of the secondary effects. Its explanation is far from clear. Colebrook and Kenny[36a] first called attention to the occurrence of sulphemoglobinemia in "Prontosil" treated cases. In 3 cases of cyanosis in which the respiratory rate was unaffected this condition was associated with the use of magnesium sulphate. Southworth[148] noted that cases treated with sulphanilamide showed a drop in the CO_2 combining power of their blood plasma, and in 2, clinical acidosis developed after large doses of the drug. Long and Bliss[95b] reported 4 cases with slight cyanosis and rapid breathing which were diagnosed as acidosis, and also 3 cases of sulphemoglobinemia. None of their patients had had saline cathartics or laxatives. Foulis and

Barr[49] had 2 cases with slight cyanosis, in only 1 of which had magnesium sulphate been given. Thomas'[151] case of streptococcus meningitis developed under "Prontosil" an extreme cyanosis with dyspnea. Schwentker[141] had a fatal case in which clinical acidosis, dyspnea, reduced CO_2 combining power of the blood and slight cyanosis developed. Long and Bliss[94c] found cyanosis in three-quarters of their patients treated with sulphanilamide, but they did not consider that it warranted stopping the treatment. In practically all their patients a fall in CO_2 combining power of the blood occurred and they recommended giving sodium bicarbonate to prevent this, and sodium lactate was used to cure and prevent acidosis. Frost[54] reported a case dying of respiratory failure in which cyanosis developed after 2 5-cc. injections of "Prontosil" and 12 tablets of "Septazine" in 2 days. Sulphemoglobin bands were found in the blood at autopsy. Magnesium sulphate had not been used. Discombe,[44] having discovered a case of sulphemoglobinemia with extreme cyanosis after sulphanilamide therapy, studied a series of 7 cases and found the former in 6 receiving over 5 gm. of the drug, and in 3 of these also a marked cyanosis. The association with magnesium sulphate is indicated in all 6 cases, in 1 the salt having been used only as a skin dressing. In 1 case, despite long use of the drug in the absence of sulphate, there were no abnormal pigments in the blood. The danger in anemic patients is suggested and the need of spectroscopic blood tests is stressed. Paton and Eaton[120] studied this problem in some detail on 20 cases and concluded that magnesium sulphate given with sulphanilamide usually gives rise, often rapidly, to sulphemoglobinemia, and without this salt the drug is well tolerated, but in some cases methemoglobinemia develops. The latter condition clears rapidly after drug is withdrawn and giving oxygen is helpful, the former may last for as long as 6 weeks and oxygen is of little value. Peters and Havard[121] had no case with cyanosis or other clinical signs suggesting sulphemoglobinemia from 215 cases treated with "Septazine." Borst[22] had a patient who became seriously ill under "Prontosil" therapy, with dyspnea and Cheyne-Stokes respirations, but without cyanosis. Whitby[161] had no case of sulphemoglobinemia in 20 cases under "Septazine." Kenny[55] had 7 cases from 47 treated with sulphanilamide in which there was methemoglobinemia without symptoms. Snodgrass and Anderson[146] reported only 2 cases of cyanosis from 160 treated with "Prontosil" and in these treatment was continued. Bensley and Ross[14] showed that methemoglobinemia is not necessarily related to dosage of sulphanilamide. They studied the hemoglobin (total, oxygen carrying and met- compounds) in a series of cases and indicated that in certain cases anoxemia may be aggravated by an anemia and methemoglobinemia. The need of spectroscopic tests was indicated in a case of pneumonia. Hageman[69a] reported cyanosis associated with methemoglobinemia in about half of their treated cases. Marshall and Walzl[99] having noted cyanosis in a large number of cases tested the blood of 7, and found in clinical cyanosis there may not be a decrease in oxygen-carrying capacity of the blood nor the presence of non-functional iron pigment (methemoglobin). Further they showed that "dark bloods" have no more than traces of this pigment, so that it can be eliminated as the cause of the cyanosis in at least 5 and probably was not the only cause in 2 other cases. They suggested as an explanation a black oxidation product of the drug staining the red blood cells. Archer and Discombe[6] concluded from their study that sulphanilamide, like phenacetin and methylacetanilide and other similar drugs, can form sulphemoglobin or methemoglobin in the blood. They are derivatives of aniline and nitrobenzene compounds and act as catalysts. The drugs with $C_6H_5N<$ in their structure are apt to cause these changes. How methemoglobinemia is formed is unknown they said, but sulphemoglobinemia they believed is formed from excess hydrogen sulphide produced by bacteria in the bowel, and that in the presence of these drug-catalysts the sulphur pigment is formed with relatively smaller amounts of the sulphide. The effect of magnesium sulphate they considered as due to the more fluid bowel contents favoring bacterial growth, and that low residue diets can to a degree control this sulphide production. They reported 3 cases, cyanotic after "Septazine" therapy and not on a low residue diet, in 2 of which sulphemoglobinemia was present. Colebrook and Purdie[37] examined the blood in 53 of 58 cyanotic patients receiving sulphanilamide and found sulphemoglobinemia in 13, methemoglobinemia in 24, and both in 8.

Anemia is a possible secondary effect and in infected cases is confusing as to its etiology. Long and Bliss[94c] had 2 severe acute anemias in patients receiving sulphanilamide. Harvey and Janeway[73] reported acute hemolytic anemia in 3 cases receiving large doses of sulphanilamide, which cleared up after the drug was stopped. Kohn[87] also had a case of this kind and considered that it must have been due to a predisposition. It is of interest that Jaeger[83] found "Prontosil Soluble" prevented to a degree coagulation of the blood, and that in Frost's[54] fatal case after a total of 10 cc. "Prontosil" and 12 tablets of "Septazine" the blood at autopsy is reported as having been dark and fluid.

Although several writers refer to the reduction in the number of leukocytes as a favorable sign in this kind of therapy, a few cases have occurred in which leukopenia was present. Massell[102] had such a case in which the white cell count fell to 3700 under sulphanilamide but slowly rose after withdrawing the drug. Plumer,[122] in a patient with subacute bacterial endocarditis (*Str. viridans* in the blood), found a sudden fall in the cell count from a previous 21,000 to 400 and the complete absence of neutrophils, the patient died with the signs and symptoms of agranulocytosis. Borst[22] had a case with a history of bleeding gums, and other hemorrhagic disturbances some years before, who while being treated with "Prontosil" died following a rather sudden drop in the white cell count. Young,[162] realizing that because of the types of infection treated by these drugs the presence of agranulocytosis if caused by the therapy could be readily overlooked, undertook the study of the leukocytes in treated cases. He reported a fatal case of agranulocytosis which suddenly developed under sulphanilamide. McIntosh[103] had a case of granulocytopenia in a baby under small doses of sulphanilamide. These are rather rare occurrences but serve as a warning against the possible harm of these compounds in certain individuals.

Effects Seen in the Skin.—The skin rashes and other cutaneous reactions are rather common secondary effects during the use of many of these drugs. An analysis of these should be made by an expert dermatologist so that we may learn more accurately the site of these disturbances and whether they are due to changes in the blood, the walls of the capillaries or in other tissues. The staining of the skin with the dye compounds is commented on in most of the early reports, but very little is said about unpleasant reactions.

Sensitivity to Light.—Gmelin[61] as well as Schreus[139] specifically mention that "Prontosil" did not increase the light sensitivity of the skin. However, under sulphanilamide therapy Menville and Archinard[109] had 4 cases in which after exposure to the sun such a sensitization was shown by severe reactions. Frank[51] reported 2 similar cases, Newman and Sharlit[115] 4 and in a note referred to 6 others, and Grosjean[65] 1. It is of interest that of the 11 cases in the last group with histories available, 7 were cases of gonococcus infections, and in a large proportion of the cases with cutaneous reactions to be referred to below this type of infection seemed to predominate. Of course, such ambulatory patients are subject to sun exposure, which may explain the incidence. Colebrook and Purdie[37] and many others have never seen this phenomenon.

Skin Rashes. Peters and Havard[121] had only 1 case with a macular rash out of 215 "Septazine" treated patients. Ley[93] reported only a slight and temporary urticaria in 2 from numerous cases treated with "Prontosil." Grütz,[68] using drugs of the "Uleron" series, recorded skin disturbances in 7, and Felke[47] with "Uleron" had only 1. Schwentker and Gelman[140] studied particularly the sulphanilamide rash. They had 10 cases from a total of 180 treated persons with an early rash, but in about half of all the cases it developed later (10 to 14 days). It was morbilliform in appearance and faded whether or not the drug was withdrawn, but more slowly if the drug was continued. It was often associated with a fever. Hageman[69a] reported that in 1 of every 6 sulphanilamide cases fever occurred, and in half of these there was a morbilliform rash. Goodman and Levy[63] had 2 cases of toxicodermatosis in gonorrheal patients, in 1 there were hemorrhagic lesions and they believed it might have an allergic basis. Schonberg[137] recorded a case in which a purpuric and scarlatiniform eruption, apparently as an allergic reaction, followed the use of sulphanilamide. Salvin[132] described, in a patient with acute urethritis, a hypersensitivity to this drug with urticaria and other lesions of a type so severe that this therapy had to be given up. Colebrook and Purdie[37] never observed morbilliform rashes nor were the mild skin reactions ever associated with fever. Finney[18] had an example of dermatitis medicamentosa in a recurrent gonorrheal case which was so severe that hospitalization was necessary. Myers[111] reported a severe exfoliative dermatitis with edema, purpura, fever, eosinophilia and other changes in a patient who had taken 88.3 gm. of the drug for a gonorrheal prostatitis. No attempt has been made to comb the literature, but enough has been mentioned to indicate the potential danger. It may appear that sulphanilamide is particularly responsible for most of these reactions, but this is probably due to the vastly greater numbers being treated with this drug.

Fever occurs in some cases and this adds a difficulty to the differential diagnoses. Long and Bliss[94c] found that "Prontosil Solution" produced but one toxic effect, namely, fever. Hageman and Blake[70] reported its occurrence in 21 of 134 cases under sulphanilamide treatment and compared the associated reactions to those of serum sickness.

Fever is mentioned by Recknagel,[125] Roth,[130] Grütz,[68] Felke,[47] Colebrook[36,37] and a number of other authors.

The gastro-intestinal tract shows certain reactions to these drugs. The preparations used for oral administration, the relative irritability, the psychic effect where the dye drugs are used, the acidity in the stomach all need to be considered. Although the pharmacologic studies showed no evidence for any effect on smooth muscle, yet the occasional diarrhea (Recknagel,[125] Bucy[28]), the desire to defecate (Colebrook and Kenny,[36a] Long and Bliss[94a]), and the frequently reported nausea, all indicate that in sick patients the effects may be somewhat different. The report of Schneider[136] on the unexpected violent reaction in the smooth muscle organs of the uterus, rectum and bladder in his case is of some interest.

The kidney seems relatively resistant, although Colebrook and Kenny[36a] reported some effects, Whitby[161] found a certain irritation from "Prontosil Soluble" and sulphanilamide, and Mitchell and Trachsler[113] had a case of hematuria after large doses of these two drugs. The most unfortunate series of deaths following the use of Elixir of Sulphanilamide-Massengill need only be referred to.[1] The kidney damage was shown to be due to the diethylene glycol content of the mixture, and the sulphanilamide was in no way responsible for the tragedy.

The nervous system, although involved in the acute toxic effects of these drugs in animals is practically never affected in man. The occasional case of dizziness, headache and similar symptoms are probably of circulatory origin. Whitby[161] merely mentioned a case that he had heard about with effects in the nervous system. Bucy's[28] case of optic neuritis is a most exceptional incident, and here the ferrous sulphate given with the sulphanilamide may have been in part responsible.

In summing up these secondary reactions it may simply be repeated that the chemical makeup of these drugs suggests possible harmful effects. The growing experience in treating patients has shown the need of appreciating the dangers potential and demonstrable, but these should not cause the splendid results of this type of therapy to be forgotten.

The Mode of Action of These Therapeutic Drugs. We have only the most superficial knowledge of the actual therapeutic mechanism of such well established and pragmatically effective drugs as salvarsan and its related compounds. Nevertheless it is evident to all that the knowledge of the mode of action of the drugs we are considering would be of immense help.

Direct Action on the Bacteria. It was evident from the very beginning that we were dealing with a type of action in these drugs rather different from that recorded for most previously used antibacterial chemicals. The original experiments of Domagk[45a] were based on the idea that chemical compounds with no appreciable bactericidal effect *in vitro* might be active against bacteria *in vivo* and that is how it turned out. Nevertheless, a great many attempts have been undertaken to demonstrate some direct destructive action and it would appear that these have failed to clearly show such an action. It is recognized that comparatively slight changes in culture media will prevent growth of many bacteria and that bacteriostatic effects are soon followed, as a rule, by the death of the organisms. It would therefore be of little value to divide sharply bactericidal from bacteriostatic effects.

Levaditi and Vaisman[92a,b,c] confirmed the work of Domagk in that they were unable to demonstrate any bactericidal action of "Prontosil" *in vitro* by various technical procedures, nor did they find any loss in mouse pathogenicity of streptococci even after prolonged contact with "Prontosil" in the test-tube at 37° C. Their assistant Deutsch showed that streptococci would not grow in either chicken plasma or embryonic juice, but if cellular elements were present growth followed with or without "Prontosil," and in the former case the cocci were fully virulent. Another assistant found the drug did not affect the growth *in vitro* of ameba. The results in their animal tests led to the theory that the drug might act on the microbe by making it more easily destroyed. This took place, they believed, through the drug's action in preventing the changes associated with adaptation to the animal body such as capsule production. It may be significant that they used in most of their experiments an animal strain of streptococcus, and since such animal strains form capsules much more often than do human strains, the presence of easily demonstrable capsules may have overimpressed them. The theory has to do with adaptive changes which make the bacteria less readily phagocytable, and should be so considered. The writer has not seen any report in which their experiment proving this theory has been repeated. They showed that streptococci previously grown in the animal body *and not in culture media* when injected into other mice were practically unaffected by "Prontosil" therapy. In an earlier article[92b] they gave some evidence that these drugs had effects against leukocidin and hemolysin but they did not develop this evidence in their more complete paper. They[92c] further noted degenerative changes in the extracellular meningococci in treated mice preceding the final sterilization of the exudate. Fourneau[50b] showed that sulphanilamide gave a definite inhibitory effect on molds and certain higher vegetable cells and contrasted this with its innocuous effect on animal cells. Domagk, in a later report,[45c] gave a table of *in vitro* tests with the two "Prontosils" showing no effect on the growth of streptococci, and added that sulphanilamide behaved similarly. He partly agreed with Levaditi's view but believed there were also other factors involved. He considered that in the first phase the drug is bound in the body to the bacteria and he noted swelling and other degenerative changes in the non-phagocyted cocci. Colebrook and Kenny[36a] did not believe the cocci are killed by "Prontosil Soluble" or by a compound formed from it in the body. They found a 2.5% solution killed streptococci in 1 to 3 hours *in vitro* but serum prevented this. The dilution of serum with the drug caused some inhibition of growth. Because their strain of streptococcus formed capsules in defibrinated blood containing the drug as well as without it they did not support Levaditi's idea. Bloch-Michel[20] found mice infected and cured were not immune to later infections. Colebrook[36b] in a number of ingenious experiments was able to demonstrate *in vitro* a certain inhibitory action by sulphanilamide against relatively small numbers of cocci, and very slight effect with serum of treated humans but not with that of mice or rabbits. Tréfouël[153] considered, since "Prontosil" had been shown to be effective against "established infections," and also, since animals respond even after the blood is invaded, that these facts were against Levaditi's idea of adaptive changes being the factor. Another finding of interest was the later deaths of treated mice which were found to be sterile and free from lesions. They also noted the absence of immunity in treated mice and were never able to demonstrate agglutinins for the streptococci. (This might suggest that an antigenic alteration had taken place.) Long and Bliss[94a] agreed with others that dilutions of "Prontosil Soluble" had no effect on the growth of hemolytic streptococci, but with sulphanilamide 1:10,000 a definite reduction in growth was observed even in the presence of 50% serum. This dilution also inhibited alpha and gamma streptococci, Types I and II pneumococci, *Neisseriæ* from the throat, *M. tetragenus* and 2 *Hæmophilus* cultures, but had no effect on staphylococcus, certain Salmonella strains and strains of *B. dysenteriæ*. These inhibitions are only effective in increasing the lag after 2 hours' incubation. They did not confirm Levaditi and Vaisman's observations on "capsules," but believed the cocci are in some way damaged before phagocytosis takes place. Rosenthal[127a] had found in 1934 that formaldehyde sulphoxylate would cure mice infected with a *single* strain of Type I pneumococcus, and that these mice were immune to the same and other strains, but this point is not mentioned in his later work[127b] with sulphanilamide. In a third report,[127c] he demonstrated both bacteriostatic and bactericidal action on pneumococci with sulphanilamide in high dilutions *in vitro* and believed this could explain its therapeutic effect, but there was no such action *in vitro* against streptococci, *S. albus* or *E. coli*. Nitti[117] showed sulphanilamide (1:1000) had a definite bactericidal effect against a small inoculum of streptococci in media which did not occur with compounds in which the sulphonamide radical was in the ortho or meta position. They also recorded a similar effect on 2 strains of pneumococci and on *B. abortus* but no effect on staphylococcus, *B. coli* or *B. typhi murium*. Buttle[31] found sulphanilamide 0.04% delayed growth a little with *S. aërtrycke* and *B. typhosus* but had a greater effect on pneumococci and streptococci. They also reported that the treated and surviving *B. typhosus* mice sometimes showed agglutinins and some immunity, which was not the case in the streptococcus mice. (It would be interesting to know which antigen of the bacillus produced these agglutinins.) Bürgers[29] was unable to demonstrate any bactericidal action by "Prontosil" or "Prontosil Soluble" on various strains of streptococci or pneumococci in the test-tube by any method, nor that a linkage with proteins in blood or serum increased this action either *in vitro* or *in vivo*. He failed to find any effect of these drugs on the hemolysin or virulence of many strains, nor did they affect capsule production by Friedländer's bacillus or Type III pneumococcus. Even after prolonged contact of streptococci with "Prontosil" *in vitro* no lessening of virulence was obtained, and he believed that the dye rapidly left the bacteria by diffusion in the peritoneal fluid of the injected mice. However, he did find evidence that streptococci stained by "Prontosil Soluble" *in vitro* became more permeable to vital staining with dilute crystal violet as compared with streptococci from infected mice after being washed and similarly stained. Staphylococci were not so markedly affected by this procedure and pneumococci not at all. Capsules could not be demonstrated on the peritoneal streptococci, but to the Reviewer that is not a very important argument against an adaptive change, but his failure to find any differences in phagocytic tests *in vitro* was important. However, he showed that streptococci treated with the drug for some hours, then washed and injected subcutaneously in guinea pigs produced reactions very definitely less than were obtained with the untreated washed cultures, and this was fully confirmed in the histologic studies. Similar studies with staphylococcus were negative. Long and Bliss[94a] could not confirm the finding that the serums of treated cases were bactericidal. They showed that streptococci continued growing in the peritoneal cavity of mice for several hours after injection, and they found no evidence that the chemical killed or injured the cocci since the exudate remained fully virulent whether or not the cultures were positive, the positive cultures were always "mucoid" or "matt," and the capsules on the cocci free in the exudate seemed unaffected. They suggested a metabolic change might make them more susceptible to phagocytosis and are quite definite in their belief that the drug effect is on the streptococci and not on the body cells. Buttle[32] had some evidence using small inocula that the blood of monkeys treated with diaminodiphenylsulphone or sulphanilamide became bactericidal for streptococci. Hawking[74] reported that trypanosomes withstand a 1:400 solution of sulphanilamide for 24 hours at 37° C. Mellon and Bambas[106] were unable to show that sulphanilamide had any effect on the dehydrogenases of Type I pneumococcus. They showed, however, that the spinal fluid of a treated case was markedly bacteriostatic for streptococci. Barron and Jacobs[11] found sulphanilamide slightly inhibited the oxidation of glucose by hemolytic streptococci and the oxidation of glucose and lactate by *B. Friedländer.* "Prontosil" had no such effects. Kenny[85] did some 96 tests with the urine of patients receiving sulphanilamide and found the bactericidal effect varied with the amount of drug in the urine. They tested a variety of strains of *B. coli* and other bacteria from the urinary tract and found that *Str. fæcalis* was the only fully resistant one. Dees and Colston[42] quoted Hill as having found that the urine of patients excreting sulphanilamide had no bactericidal activity against beta hemolytic streptococci. Helmholz[76] found the drug excreted in the urine had a decided bactericidal action, particularly in alkaline urine against urea-splitting organisms such as *Proteus ammoniæ*, as well as *B. coli* and *B. aërogenes. Str. fæcalis* was also found fully resistant. Mellon and Shinn[107] confirmed Helmholz's results with a 1:10,000 concentration of the drug in urine and recorded the important observation that if urine is added to the initial media, the diluents and the test media, the bacteriostatic and bactericidal effect on *B. coli* is more marked than if broth alone is used. Mellon had previously found a similar potentiative effect with saline using hemolytic streptococci, in that dilution in saline solution enhanced the bacteriostatic effect of the drug and in the presence of normal human serum this effect was further increased. These results give a correlation between *in vitro* tests and *in vivo* clinical results. Gay and Clark[58] found that sulphanilamide had only a bacteriostatic effect in pleural fluid infected with streptococci, and that it never by itself sterilized it. They noted distinct degenerative changes (variation in size and metachromatic staining) in the streptococci under the influence of the drug in serum, and cultures from treated pleural exudates showed some increase in "matt" over "mucoid" colonies but only in the primary culture. The virulence was unaffected. Bliss and Long[19b] in a study of this problem concluded that inhibition of growth *in vitro,* and a change in the bacteria permitting their phagocytosis *in vivo,* are the only real direct effects produced by sulphanilamide. They failed to demonstrate in the streptococci from treated mice any alteration in type of colony, virulence or capsule formation. Experiments in mice infected intraperitoneally with *B. welchii* and treated by the drug showed the bacteria to be inhibited, and this reduction in multiplication to a rate at which there cannot be produced enough "leukocidin" or other toxins to inhibit rapid phagocytosis explained, they believed, the curative effects in these as in the other bacterial infections. The evidence from the *B. welchii* experiments is somewhat difficult to evaluate. This organism readily forms capsules in the body. The untreated mice died after a few hours obviously from toxemia. Phagocytosis began almost at once. The drug was given before the inoculation. The periodic study of the peritoneal exudate showed marked phagocytosis in both groups at first. As the number of free bacteria in the untreated mice increased so did the number of those phagocyted. In the treated the numbers of both free and phagocyted bacteria decreased. Capsules are not mentioned but there is no evidence that their production did not play a part in the results recorded. This experiment of peritoneal infection with *B. welchii* is not of course directly comparable to gas gangrene in man in which the inhibition of phagocytic action is manifest. However, this experiment clearly demonstrated the striking bacteriostatic effects of the drug.

It is evident that under certain conditions the growth of bacteria is detrimentally affected by these drugs both *in vitro* and *in vivo.* This is indicated by morphologic changes and by inhibitory and even bactericidal effects, but these effects, although seldom strikingly demonstrable, may nevertheless be of primary importance for the final destruction of the bacteria by the defense mechanisms in the body.*

The Effect of These Drugs on the Body Defenses. It is generally accepted that the body defenses are the important and necessary factors in the final curative effects of this type of therapy, and most of the clinical reports emphasize the danger of relying solely on the action of any of these drugs. However, it is not at all clear what actually are the effects of these compounds on the defensive mechanism. That there may be harmful secondary effects is evident from the discussion already given but whether stimulations or other benefits result from their use is undecided.

Domagk[45a] stressed the part played by the neutrophils and the monocytes, as have many others since. Levaditi and Vaisman[92c] showed that these drugs do not prevent the growth of fibroblasts and other cells in tissue cultures. The inconstancy of their experimental results clearly indicated that they were dealing with individual differences in the sensitivity or resistance in their mice, and that the balance of bodily defense is often unstable so that late deaths in treated mice sometimes occurred. Domagk later[45c] showed that the inhibitory effect on bacterial invasion was important and suggested that the monocytes may be activated. Jaeger's[83] results showed "Prontosil" acted locally and he gave some evidence that it stopped excess exudate, changed the character of the pus, softened the wall of abscesses, had an astringent effect, helped the coagulation of blood ("Prontosil Soluble" did not) and like other azo dyes favored granulation tissue. He cited the rapid decrease in the edema in erysipelas as suggestive of the drying effect of "Prontosil." Tréfouël[155] mentioned the finding of cocci in the blood after treatment, and although these bacteria disappeared under further treatment the animals usually died but showed no streptococcal lesions. Long and Bliss[94] believed that the neutrophils at first and the monocytes later were the factors which finally control the infections. In their experiments the drugs were not given until 8 hours after injection of the streptococci and they recorded that all but 4 of 102 mice had positive blood cultures 12 hours after the intraperitoneal inoculation. This may explain why they had so many late deaths in these treated animals. Mice are very sensitive to streptococcal infections and a number of spontaneous epidemics in laboratory mice have been reported, so that there is just a possibility that some of these late deaths may have followed a reinfection by cage contact. Berger's studies[15] on subcutaneously infected mice led him to consider the effects of the drug on abscess formation. He found very little effect on the primary reaction, a certain degree of limitation and a more rapid evolution of the process but quite definitely a prevention of septicemia. Rosenthal[127b] working with sulphanilamide and pneumococci found a much more marked localization of the infection in the mice in which life was prolonged by the drug and there were fewer cocci found in the blood in these mice than in the untreated controls. Bürgers[29] stressed the increase in cellular defense as an individual factor of first importance, and this was indicated by differences in survival among different races of mice and at different times of the year. He also found that mice dying after treatment often had sterile organs. In rabbits, infections were cured even when treatment was delayed 2 to 3 days but not after the fifth day. Gross and his associates[67] did not find that splenectomy prevented the protective action of sulphanilamide in mice given highly virulent streptococci, and the degree of protection was the same as that obtained with normal mice. They recorded that 2 of the splenectomized mice dying after treatment gave negative cultures at autopsy. Long and Bliss[94c] described the wave of neutrophils which appeared in the treated mice 6 to 15 hours after the streptococci were injected intraperitoneally. Cooper and Gross[39a] found in experimental Type III pneumonia in rats that the treated rats which succumbed had bacteremia and peritonitis less often than the untreated fatal cases. Mellon[103] did not find an indication that phagocytosis is a factor in the mechanism of the therapeutic action of these drugs in mice infected *via* the peritoneum with hemolytic streptococci. In guinea pigs, intradermal infections remained localized and rapidly healed in the treated animals, and the histologic response was found to be qualitatively the same as in those with a fatal outcome. The rapid disappearance of pus in treated cases of acute gonorrhea may be illustrated by the results of Dees and Colston[42] as well as by many others. Hofmann[77] found that "Prontosil Soluble" injected into the muscle of dogs penetrated sterile turpentine abscesses as long as these were developing, but these became impermeable to the dye as soon as they were no longer progressive.

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* Levaditi and Vaisman showed antiendotoxic effects with certain sulphone and sulphoxide drugs (Table 1).

These experiments were done in an attempt to explain the failure of this chemotherapy in established abscesses in man. An interesting observation was that 2 dogs with active abscesses suffered from evident loss of appetite and seemed depressed, but these symptoms rapidly improved when the drug was given. This certainly suggests some general effect. Kreidler[90] reported that 1 of 2 rabbits, after an endodermal injection of pneumococcus and not treated until 48 hours, died 9 days later with the local lesion healed and a negative blood culture at autopsy. Basman and Perley's[12] speculation as to the cause of abscess formation in cases of erysipelas has been mentioned above. It is another example of the localizing effect of these drugs. McKinney and Mellon[104] undertook a study to determine the relative importance of the neutrophils and monocytes in this problem of phagocytosis and were able to show that marked differences in cell response followed the injections of different strains of streptococci (Group A). Some mucoid strains are readily taken up by neutrophils, others seem to need macrophages, but the phagocytosis of virulent strains is conditioned by the previous bacteriostatic action of the drug. Bliss and Long,[19b] chiefly on the basis of their results in *B. welchii* peritonitis in that they did not find any decrease in phagocytosis in the untreated mice up to the time of death (a few hours), did not believe the drug stimulated phagocytosis nor that it protected the cells from the products of the bacteria. The need of the leukocytes in the curative process against streptococci was made evident when these cells had been previously reduced by injection of benzene to below 500 per c.mm. of blood, since such mice could not be protected against streptococci by the drug. Gay and Clark[58] studied the problem by experiments in the pleural cavity of rabbits, using a technique perfected by many years of experience. They believed sulphanilamide is a preventive and not a true curative drug. In empyema induced by injections of virulent streptococci blood stream infection was prevented by the drug, the leukocytic count increased as contrasted to a decrease in the controls, the amount of pleural exudate was markedly less and the growth of the streptococcus was greatly reduced. The first cells to appear in both groups were the neutrophils, but in the treated animals the monocytes increased after 36 hours and by 48 hours were predominant. Monocytes were not stimulated *in vivo* by the drug, either in the presence of sterile exudate or killed streptococci. They were found by histologic studies to be massed after 36 hours in the septa and subserous layers of the pleura and some were seen in active mitosis. This accumulation of monocytes was not so striking at the 48-hour period when the pleural cavities became sterile but appeared in quantity from 4 days onward. The course of events in the treated animals was outlined as a bacteriostatic action of the drug, the outpouring of leukocytes and finally for complete sterilization the coöperation of monocytes derived from the local tissues.

The direct transfer of the results from animal experiments to the explanation of the occurrences in human infections is, of course, not justified. In the experimental studies, the most sensitive animals are chosen and the most virulent strains of bacteria are used. There are no preliminary contacts between germ and tissue as happens in the stages of invasion, and the mobilization of defenses to be effective must be very rapid. There is much evidence scattered through the references

I have cited to indicate that the sulphanilamide type of therapy is most effective in the progressive stages of an infection in which active and continuous tissue reactions are taking place. The drug under such circumstances would seem to add the necessary bacteriostatic effect which often tips the balance in favor of a cure. The combined use of antiserum and drug should theoretically add to the curative effects as it has experimentally and practically in a few cases, since antibody defense is often a necessary factor in cellular defense.

The possible general effects of this group of drugs should be more thoroughly studied. Do they in any way affect the inflammatory reaction? Most of the pathogens grow in the interstitial fluids which, if excessive in unchecked inflammation, may embarrass the nutrition of the local tissue cells. Can these chemicals affect the edema of inflammation as has been suggested? Phagocytic cells have been held responsible on excellent experimental evidence for the transfer of pathogenic bacteria to various parts of the body. Leukocytes, in addition to their well established function in phagocytic destruction of bacteria have also high enzymatic activities which are known to injure tissue cells partly by depriving these cells of a portion of their food and partly by direct more or less toxic effects. Further, leukocytes by their action on serum proteins and other substances may provide more easily available nutrients for certain bacteria despite their injurious effect on ingested organisms. Do these drugs have, perchance, a regulating effect or do they prevent an excessive leukocytosis? The clinical findings suggest that on occasion these cells may be disastrously affected and it has been suspected that this is due to the benzene nucleus. It may be that the drugs still retain some of this effect of benzene in a much milder form. Whether these studies may throw some light on the varying infectious processes characteristic for different groups of bacteria the future will determine. There are innumerable problems still to be solved. Some of these comments are admittedly mere speculations, but until we know more exactly the mode of action of these substances, so remarkably effective in chemotherapy, guarded speculation may be justified.

No conclusions are advisable at the present stage of this complicated study. New compounds are constantly appearing which must needs be evaluated. Excellent experimental and clinical methods of study have been evolved, and the future looks bright for even greater progress in this opening field of chemotherapy of bacterial infections.

While this article was in press there appeared the important report by Dochez and Slanetz (Science, 87, 142, 1938) on the successful Treatment of Canine Distemper—a virus disease—with sodium sulfanilyl sulfanilate.—EDITOR.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
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SOME RECENT ADVANCES IN DIPHTHERIOLOGY.

ALTHOUGH the field of diphtheria has been the scene of brilliant and epoch-marking discoveries, such as those of Loeffler[39] who isolated the diphtheria organism in 1883, Roux and Yersin[60] who demonstrated the exotoxin of the organism in 1888, and of v. Behring and Kitasato[4] who developed antitoxin in 1890, the physician of today, called to treat an acute inflammatory condition of the throat, is still confronted with much the same problems that have beset clinicians for many decades, even though diphtheria was clearly defined as a pathologic entity as early as 1821 in the classical memoirs of Brettoneau.[7] The modern doctor finds, in addition, that a case of diphtheria is no longer a purely clinical and scientific problem but may also involve sociologic questions arising from administrative regulations. Confronted with these difficulties, the busy practitioner naturally looks to the research worker, in the field and in the laboratory, for new or improved instruments or methods with which to overcome them.

From a purely clinical and therapeutic standpoint relatively little of a fundamental nature has been added to the armamentarium of the physician in recent years except the familiar concentrated and purified antitoxin and certain improved supportive and palliative measures which are matters chiefly of pharmacy and materia medica.

From a more abstract, but nonetheless practical point of view, a number of advances have been made recently which place in the hands of the physician and laboratory worker improved means of determining the presence of diphtheria bacilli in the throats of patients and healthy persons, of isolating them, of determining their virulence and biologic type, and of immunizing susceptible persons.

Bacteriologic Diagnosis. Of immediate interest to the practitioner are those researches dealing with the most rapid and accurate means of obtaining information as to whether or not the throat of his patient harbors diphtheria bacilli; and, if so, whether they are virulent or avirulent. Unfortunately, this particular field of bacteriologic research offers relatively little of which to boast. The cotton swab, rubbed on a slant of Loeffler's medium which is incubated overnight and examined microscopically next morning, still continues as the standard diagnostic procedure. A more rapid but possibly less accurate means of demonstrating the presence of diphtheria bacilli in the nose or throat has recently come into prominence and consists of a sterile swab, dipped into sterile fluid Loeffler's mixture (or plain serum) and then held over a flame just long enough to coagulate the serum. This is rubbed over the patient's throat or nasal passages in the usual manner and then inserted into a sterile, plugged tube or vial. Growth of the bacteria from the respiratory passages may occur on the serum at the temperature of the physician's vest pocket (30 to 35° C.) in 4 to 8 hours, after which a smear made directly from the swab may show the diphtheria organisms. Longer incubation at 37° C. is desirable when circumstance permits. The idea was originated by Folger[19] and modified (1934) by Solé[67] and later by Brahdy, Brody, *et al.*[6] Unfortunately, the swabs dry out rather quickly before or after use and the serum is apt to crumble in the patient's nose or throat.

A few staining methods designed to render the metachromatic granules (volutin?) of the organisms more prominent were in vogue some years ago; but due to the fact that volutin, or some similarly staining substance, is common to many cocci and other organisms, most competent workers now recognize that these stains often lead to false diagnoses. The methylene blue stain (which has been greatly improved by modern synthetic chemistry) is today more reliable and uniform than ever, and the staining method of Loeffler is still adhered to by conservative and careful bacteriologists.

Possibly we have only recently come to realize that there is a large number of hitherto undescribed forms which may be assumed by the capricious diphtheria bacillus; but it is doubtful if the older workers failed to see these, whether or not they recognized and described them. The "atypical" forms are practically always accompanied by enough typical organisms so that, in a pure culture, they are easily recognized for what they are. However, Van Volkenburgh and the writer[26] have recently brought forward evidence suggesting that in original throat cultures, especially those from healthy carriers, the diphtheria bacilli may be present in large numbers, yet demonstrable only after isolation in pure culture. The data indicate that a negative smear frequently does not prove the absence even of large numbers of *C. diphtheriæ* and that the organisms may be present only in the recently described coccoid forms[34,68] which are almost impossible of recognition in throat cultures containing staphylococci, streptococci and neisseriæ.

The Virulence Test. With respect to the determination of the virulence of diphtheria organisms, the intracutaneous, pure-culture method of Eagleton and Baxter[18] remains the standard technique in most laboratories. A more economical intracutaneous method, designed by Fraser and Weld,[24] is being given some prominence at present. It is described by Fraser and McNabb in the A. P. H. A. Year Book for 1936–1937 (p. 121). Several pure culture suspensions may be injected into the shaved dorsal skin of a rabbit or guinea-pig in 0.1 cc. amounts. After 4 to 7 hours about 500 units of antitoxin are injected intravenously or intracardially and the same doses of the same suspensions are immediately afterward reinjected in sites near the original ones. The damage done in each *original* injection site during the 4 to 7 hours when the rabbit was unprotected by antitoxin is not repaired by the antitoxin and later develops into a typical lesion. The second injection site remains normal and serves as a specificity control. The saving in animals is the principal advantage of this method, as it is subject to the errors which are inherent in all intracutaneous work. The use of the mixed (or "whole culture") method[20,32] is deprecated today except as an emergency, or purely secondary and confirmatory, measure and it is now recommended that it be used, if at all, only in connection with known clinical cases. The most reliable virulence test is undoubtedly the classical method consisting of the *subcutaneous* injection of 0.5 to 1 cc. of a heavy saline suspension or broth culture of *one strain* of organism into a normal, 250 to 300 gm. guinea pig and into an antitoxin-protected control. Death of the normal pig, or the appearance of a definite local lesion, and complete absence of any change in the control is evidence of virulence. It might be of interest to note, in passing, that recent studies[3,51,57] on the persistence of virulent organisms in the throats of convalescents show quite conclusively that true diphtheria bacilli tend to retain their virulence indefinitely and that the variation of an organism from toxigenic to non-toxigenic must be an extremely rare occurrence. A few instances of the latter appear in the literature;[12,13,44,70] but they are few indeed and much cited and in some of the evidence one may, perhaps, detect that nemesis of the laboratory bacteriologist—contamination. It is probable that diphtheroids become implanted in the normal throat after the cessation of convalescence and that they have often been mistaken for avirulent diphtheria bacilli derived from those originally present during the pathologic condition.

Improved Methods of Cultivation. Since determinations of virulence, as well as scientific studies, necessitate the isolation of diphtheria bacilli in pure culture, numerous attempts have been made to facilitate isolation by means of selective plating media. Many of these media have also been proposed as substitutes for Loeffler's in primary diagnostic work. In the latter field, however, Loeffler's medium has so far held its own against all competitors, although, for primary diagnosis and general cultural work, a simpler medium consisting of 3 volumes of hens' eggs well mixed with 1 volume of water or normal salt solution, was devised a few years ago by Pai.[52] In the writer's hands, at least, it has been found to be the equal of Loeffler's medium in all respects.[41] Its chief virtue lies in the fact that one can obtain eggs readily at almost any time or place, in any amount; a fact in contrast with the difficulty which is often encountered in obtaining and storing quantities of serum as well as the time and expense of preparing dextrose-infusion-broth with which to mix it.

With regard to the isolation of *C. diphtheriæ* in pure culture, the use of minute amounts of potassium tellurite in blood or serum agar for plating media has been found most useful. The tellurite prevents or retards the growth of many of the saprophytic organisms normally contaminating throat swabbings and, in addition, confers a more or less characteristic appearance and a black color on the diphtheria colonies. Although the value of tellurium salts for such work was recognized as early as 1912 by Conradi and Troch,[10] it first received world-wide notice following the researches of Clauberg,[8a,b] who at first devised a somewhat complex and cumbersome medium containing glycerin, blood and tellurite. Numerous modifications were later made, nearly all of which tended toward simplification. Possibly the simplest and most generally valuable modifications are those devised by McCleod *et al.*,[1] by Douglas,[16] and by the writer.[25] The latter consists merely of 5% blood agar to which is added about 0.04% potassium tellurite and 0.005% cystine; the cystine has been shown by Schmidt[63] and others to be essential to the growth of the organism because of its sulphydryl group (SH).

Opinion differs as to the advisability of using such selective media in place of Loeffler's or Pai's for primary diagnostic work. Cystine is is known to distort the morphologic appearance of *C. diphtheriæ* so as to render the organisms almost unrecognizable except by the expert while tellurite, being very toxic, may well prevent growth of the diphtheria organisms when the swab contains very few of them to start with, especially since, coming freshly from the throat, they find on tellurite agar at best a somewhat strange and inhospitable environment. This is notably true in dealing with healthy carriers. However, many workers,[1,31,62] especially in Europe, are now using as a routine procedure the inoculation of plates of some variety of tellurite medium directly with throat swabs and basing their diagnosis on the appearance or non-appearance of diphtheria colonies, which are generally characterized by a gun-metal or black color and can be recognized (usually) by one familiar with them. When growth occurs, isolation is of course advanced by 24 hours. It has recently been shown,[26,27] during surveys of school children, that by first inoculating Loeffler's medium and, after 18 hours' incubation, smearing the growth on cystine-tellurite medium, the number of carriers detected may be greatly increased over those found by the mere microscopic examination of the growth on the Loeffler's tubes.

Gravis and Mitis Types. The organisms isolated during the surveys referred to above were found to be rather uniform in their cultural characters, but this has not been the experience elsewhere, and biochemical differences between strains of *C. diphtheriæ* isolated from different types of cases have been the subject of world-wide discussion for several years. In 1931, Anderson, Happold, *et al.*[1] described two types of *C. diphtheriæ* which they called, respectively, *C. diphtheriæ gravis* and *C. diphtheriæ mitis.* The former was said to be characterized by its fermentation of starch and glycogen; the formation (on McLeod's "chocolate" tellurite medium) of a distinctive type of rough colony; a peculiar, diphtheroid-like morphology; absence of hemolytic power; ability to form pellicles on broth, and a rapid alkalinization of broth. The mitis types had characters generally the opposite or negative in these respects, fermenting neither glycogen nor starch, producing smooth colonies, a typical morphology, no pellicles, demonstrable amounts of hemolysin and slow alkalinization of broth. *C. diphtheriæ gravis* was found associated with severe, fulminating and often fatal cases, while the mitis types were usually found in mild cases and in healthy carriers, and were frequently avirulent. A type spoken of as "intermediate" was described on the basis of only 6 cultures and resembled the mitis type except for a slight flatness in colony form and a granular growth in broth, both of which are trivial differential characteristics. A great deal of work was done following the original report of Anderson *et al.* The reader interested in detail is referred to the list of references appended hereto.[11,45,46,54,58,61,72]

As is all too frequently the case, subsequent workers have disagreed with the original reports of Anderson *et al.*, and also among themselves. One very obvious reason for the diversity of opinions in this instance is that each worker has set up his own definition of the *gravis* and *mitis* types and it is impossible to compare any two sets of data so far reported in the literature on exactly the same basis. From the welter of confusing evidence, however, and judging by the writer's own experience, the conclusion seems indicated that gravis-like and mitis-like types are encountered, but that all of their distinctive characters are variable, that they often tend to vary toward the opposite type with regard to any cultural character, both *in vitro* and in nature, and that no one or more biochemical characteristics (including starch fermentation) are necessarily associated with the clinical severity of any case of diphtheria. Starch fermentation, a widely used differential test, is especially subject to experimental error. Further, the determination of type is of no clinical or prognostic value because of the time required. Studies of type do seem, however, to have a distinct usefulness in following the epidemiology of diphtheria.

The toxins of the various types seem to be qualitatively identical,[46,54,55] although strangely enough the gravis strains are sometimes poor toxin producers (*in vitro*) as compared with mitis.[42,43] However, it is possible that certain strains, such as the gravis type, may possess enhanced powers of maintaining themselves in the throat in spite of antitoxin therapy or that, in the human throat, certain toxic substances are produced which do not appear in artificial culture media.

Active Immunization. With regard to active immunization against diphtheria some notable achievements of recent years may be cited. Shortly after the work of Behring and Kitasato (1890) (probably at the suggestion of Theobald Smith) it became the general practice to use, for the immunization of children against diphtheria, small amounts of diphtheria toxin which had been *almost* completely neutralized with antitoxin. Three injections of 1 cc. of such mixtures, given at weekly intervals, were required. The method was effective but cumbersome and there were some accidents resulting from improperly neutralized toxin and from a dissociation of the toxin and the antitoxin due to freezing. However, "T. A. T.," as the immunizing mixture was familiarly called, was for years widely and successfully used.

A distinct advance in the fight against diphtheria was made in 1921 when it was observed by Glenny and Sudmerson[29] that diphtheria toxin which had lost its toxicity with the passage of time, or as a result of the action of various agents (such as heat, light, or chemicals, especially *formaldehyde*) was still just as *antigenic* as the toxin from which the detoxified product (toxoid) had been prepared. The advantages in using such material as an immunizing agent in the control of diphtheria.[56b] were realized by everyone in the field; but the name of Ramon in France is prominently associated with the exploitation of formalin-toxoid or, as he called it, "anatoxin." Potent, toxin-containing broth is treated with about 0.4 % of formalin at 37° C. for 4 to 6 weeks. The material is then tested for loss of toxicity and for antigenic power and is sold as toxoid. The formalin is believed to combine with some part of the toxin molecule so that toxicity is lost but specific antigenic properties are retained. Whatever the explanation may be, many scientists confirmed the work of Glenny, Ramon, and their colleagues. Ramon[56a] also showed that the formalin toxoid could be flocculated promptly and quantitatively by an exactly neutralizing quantity of antitoxin, for example, 1 unit (hence the "L f dose" or "flocculating unit" of toxoid), and it could, like toxoid, be standardized by this means. Two or three 1 cc. (12 to 15 L f) doses of the formalin-toxoid were found by many[15,23,37] to be as effective in immunizing as the T. A. T. and yet obviating the dangers inherent in the latter.

One difficulty with toxoid was (and is) that disagreeable reactions occur in many children of about 7 years of age, or over. These are believed by many to be of an allergic nature due to the proteins of the meat, peptone, or bacterial cells used in preparing the cultures. Others ascribe them to the toxoid itself. Probably both are involved. Therefore attempts were made to remove the extraneous substances from toxoid broth by flocculation and precipitation methods, applying the knowledge gained as early as 1902 by Danysz[14] that various precipitates adsorb toxoid. Antitoxin, as a flocculating agent, was known to be effective, but, of course, introduced still more foreign protein. However, it was observed by Glenny and Barr[28] that the precipitate which potassium alum formed upon its addition to toxoid-containing broth, adsorbed and held all the toxoid. Wells, Graham, and Havens[71] and later Havens and Wells[33] purified such alum-precipitated toxoid by removing the supernatant fluid, washing the precipitate in saline solution and then resuspending it in a volume of saline solution equal to the original toxoid. The milky fluid thus obtained was found to contain practically all of the original toxoid and was said to be a more effective immunizing agent than the anatoxin of Ramon. Evidence has since been brought forward[2,40] indicating that 1 dose of this alum-precipitated toxoid has the same immunizing value as 3 doses of T. A. T. or of unprecipitated toxoid, and in some fields it has come to supplant the latter two. However, it is still subject to the same objections as the old formol-toxoid; *i. e.*, the frequent occurrence of sometimes severe (but usually local) reactions in older children. The alum itself may have some part in this effect. On the other hand, there are competent authorities[22] who hold the anatoxin to be the superior antigen, and indeed the matter needs further elucidation.

One advance of some importance resulted from various studies of the allergic reactions referred to above. It has been customary to use, as a control in the Schick test, exactly the same material as is used for the test itself, but heated at about 80° C. for 15 to 30 minutes. Moloney and Fraser[49] tried formol-toxoid as a control in the Schick test. They observed numerous pseudoreactions but found them to occur chiefly in persons who were likely to react severely against immunizing doses of toxoid. By the use of a preliminary intradermal injection of a *suitable dilution of a selected toxoid*, therefore, it was found possible to avoid severe reactions in persons sensitive to toxoid. The "Moloney test," as it is called, is still under investigation, both as a control for the Schick reaction and as a guide in toxoid immunization.[48,69]

The immunizing efficacy claimed for alum-precipitated toxoid is ascribed to a continuous and *prolonged* stimulation of antibodies due to slow absorption of antigen, by the tissues, from the surface of the particles of alum precipitate in the locus of the injection. The original fluid toxoid of Ramon is very quickly absorbed and excreted and its stimulating action, being transitory, has to be applied repeatedly in the form of 2 or 3 successive doses.

This rapid absorption of the soluble material may have been the principal reason for unsatisfactory results at first obtained with very pure and highly concentrated (50 to 70 L f per cc.) toxoids developed by Schmidt and his collaborators,[65,66] using aluminum hydroxide as the precipitant and then redissolving the toxoid in small volumes of Na_2HPO_4 solution. The rate of absorption of this fluid product was later retarded by mixing a small amount of $Al(OH_3)$ with the purified, concentrated toxoid.[64] Leach, Jensen,[38] and others report very satisfactory results with the latter antigen; a single dose of 1 or 2 cc. (35 to 50 L f per cc.) producing immunization in a large percentage of children tested, with minimal untoward reactions.

Coincident with these studies Jensen and others, using a modification[21,35] of the intracutaneous serum-antitoxin-titration method originated by Römer,[59] have reinvestigated the relation between the Schick reaction and the serum antitoxin titer, the rate of immunization, and the rate, duration and decline of immunity of individuals and populations of different age composition, sex, color and previous natural and artificial contact with diphtheria bacilli, toxin or toxoids. Many other studies bearing on the problems of diphtheria control have also been possible by this means, and a great number of interesting and important facts have thus been brought to light. For example, Michiels and Schick,[47] investigating the relationship between the Schick reaction and the antitoxin titer in human serum, had earlier arrived at $\frac{1}{30}$ to $\frac{1}{50}$ unit per cc. of patient's serum as the quantity of antitoxin necessary to give a negative Schick test. Persons whose serum contained less than $\frac{1}{30}$ to $\frac{1}{50}$ unit per cc. generally gave a positive Schick reaction. More accurate studies of v. Gröer and Kassowitz,[30] recently confirmed by Fraser, Jensen, and others have since shown that $\frac{1}{250}$ unit is more nearly the level at which the Schick test changes from positive to negative. It seems likely that the later workers used purer toxin, which had less of the impurities tending to interfere with, or non-specifically to combine with, the serum antitoxin of the patient.

Black,[5] in 1934, published data suggesting that colored children respond more quickly to the antigenic stimulus of T. A. T., and therefore, inferentially, of toxoid and of actual infection, than white children. Further, individuals of either race have been found to show marked personal differences in immunizability or rate of response to diphtheria antigens. This is of importance epidemiologically and clinically. Obviously, a child whose body responds by the production of antitoxin a few hours after diphtheria bacilli have lodged in its throat is less likely to contract clinical diphtheria than children who respond slowly or not at all.

The effect of a primary and a secondary stimulus on the rate of antitoxin production by human beings has recently been under investigation and an interesting and promising method, not only of inducing but also of *maintaining* immunity in a population, even including the immunologically refractory individuals, and involving only a single subcutaneous injection of toxoid, has been brought forward by Jensen.[35]

The method is based on an immunologic phenomenon originally observed by Cole in 1904,[9] who studied the immune reactions of rabbits being injected with typhoid bacilli. In animals whose tissues had once been in effective contact with typhoid bacilli but whose agglutinin titer had fallen very low with the passage of time, it was found that the original high titer quickly (in a few hours) returned following a single small injection of the specific antigen. The phenomenon seems to be of broad, fundamental significance and its occurrence is probably to be observed in connection with many other antigens. In any event it has been observed in the case of diphtheria toxin; so small a stimulus as the Schick[17] test having a prompt and well-marked effect on the antitoxin titer of the blood serum, especially in persons whose tissues have already had some experience (primary stimulus) with diphtheria bacilli or their toxic products.

The method of immunization proposed by Jensen is based on these observations and consists of a primary injection of 1 to 1.5 cc. (≡35 to 50 flocculating units) of Schmidt's purified and concentrated toxoid mixed with 10 volumes % of a special $Al(OH_3)$ suspension. This constitutes the "primary stimulus." It is followed after an interval of 4 weeks, by 3 to 6 *intranasal* instillations, of 25 flocculating units each, of the clear $Al(OH_3)$-free concentrate, given about 2 to 7 days apart. These constitute the "secondary stimulus." The immunity response has been found highly satisfactory in all cases tested; disagreeable reactions to the first injection being relatively slight, and those to the subsequent nasal instillations *nil.* The possibility of leaving the instillations to the mother after the first injections are made, is pointed out. There are obviously many aspects of this problem which remain to be worked out in detail. Recognition of the fact that a primary stimulus prepares the tissues so that they respond promptly to any ordinary infection is, however, an important advance. The relative rarity of diphtheria in adults, even though many are known to be Schick positive, is probably dependent on their ability to mobilize their defenses almost instantly upon invasion by a toxigenic organism.

New Media for Toxin Production. We may close this survey with a brief paragraph concerning the researches of Mueller,[50] Pappenheimer[53] and their associates, on the metabolic requirements of *C. diphtheriæ*, which have culminated in one of the most fundamental and suggestive discoveries made in recent years. One of the great obstacles to an exact knowledge of the growth and functioning of bacteria and their toxins, both in the human body and in the test tube, has been the fact that as far as was known the organisms would grow and produce toxin only in broth containing such empirical and variable mixtures as peptone and meat infusion. After a long series of experiments, a medium was finally prepared consisting *only* of pure water and pure chemical compounds of *known* formula and origin, such as glycine, cystine, pimelic acid, $MgSO_4$, nicotinic acid, NaCl, and so forth; a synthetic medium in brief, in which diphtheria bacilli will grow abundantly and produce relatively enormous quantities of toxin. The value of such a discovery is immediately apparent not only in diphtheriology but in other branches of bacteriology. It seems very likely that in the near future the present methods of preparing antigens for the prevention of diphtheria and other diseases will become obsolete as a result of this work. Only time can reveal the greatest significance of such studies as these.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 17, 1938

The Action of Sodium Bisulphite and Sulphanilamide on Purine and Pyrimidine Compounds With the Production of Hemolysins, and a Suggested Mechanism of the Action of Sulphanilamide on Hemolytic Streptococci. E. J. CZARNETZKY and M. G. SEVAG (Department of Bacteriology, School of Medicine, University of Pennsylvania). Hope of finding a chemical entity capable of destroying bacteria specifically without injury to the host seems to have been realized in the discovery of the action of sulphanilamide on streptococci. In order to take advantage of this finding in a search for new specifics which would combat other types of bacterial infections, it is necessary to determine the basic chemical reactions underlying the bacterial action of sulphanilamide.

There is good evidence for the belief that the surface of β-hemolytic streptococci of Lancefield's Group A contains an antigen which is partly composed of nucleic acid. This antigen can be isolated in a purified form, and when treated with sodium bisulphite or sulphanilamide it becomes lytic for red blood cells *in vitro*. Yeast nucleic acid and vitamin B_1 are made hemolytically active in the same manner by both reagents. It is known that the reaction between vitamin B_1 and sodium bisulphite results in the formation of a sulphonic acid derivative of the pyrimidine ring of the vitamin. Such a sulphonic acid derivative is hemolytic. Whether a similar chemical reaction takes place between sodium bisulphite and yeast nucleic acid or streptococcal nucleic acid, resulting in the production of hemolysins, has as yet not been verified.

A consideration of the toxic effects of sulphanilamide which include hypochromic anemia and granulopenia seems to be in harmony with the fact that sulphanilamide may react with nucleic acid compounds with a resultant formation of hemolysins.

The possibility that inorganic sulphites might be substituted for sulphanilamide in the chemotherapy of streptococcal infections is being investigated.

The Use of Lyophile Plasma in Correcting Hypoproteinemia and Preventing Wound Disruption. W. D. THOMPSON, JR., I. S. RAVDIN, and I. L. FRANK (Laboratory of Surgical Research, University of Pennsylvania). In previous experiments in hypoproteinemic dogs we observed a high incidence of abdominal wound disruption after laparotomy. The present experiments were devised to determine whether wound disruption in hypoproteinemic dogs could be prevented if the hypoproteinemia was corrected by the intravenous administration of serum after laparotomy. In such animals, the serum protein level was normal within 7 days following operation. Fibroblastic proliferation progressed at a normal rate in these animals and complete repair was present within 14 days.

The Effects of Pressor Drugs and of Saline Kidney Extracts on Blood Pressure and Skin Temperature of the Rabbit's Ear. EUGENE M. LANDIS, HUGH MONTGOMERY, and DONALD SPARKMAN (Departments of Pharmacology and Medicine, University of Pennsylvania). Many pressor substances have been studied to determine their effects on blood pressure, relatively little attention being paid to their action on the peripheral blood-vessels. It has been shown recently (Prinzmetal and Wilson, Pickering) that in human hypertension abnormally high blood pressure is associated with normal peripheral blood flow, even when vasoconstrictor tone in the extremities is diminished by warming the body. It seemed highly desirable, therefore, to determine whether the action of known pressor substances simulates human hypertension to the extent of producing, in an experimental animal, a rise of blood pressure without reducing peripheral blood flow simultaneously.

The usual oscillometric technique was modified to permit photographic recording of systolic blood pressure and pulse amplitude in the central artery of the rabbit's ear while vasoconstrictor tone of nervous origin was abolished by warming the body of the rabbit. Changes of peripheral blood flow were determined by measuring skin temperature. This procedure (1) did not require anesthesia, (2) excluded spontaneous variations in vasoconstrictor tone, (3) avoided trauma of the vessels studied, (4) permitted repeated observations on the same animal over periods of days, and (5) allowed slow intravenous injection of drugs or extracts at a constant rate over long periods of time.

Adrenalin, tyramine, pituitrin, pitressin, ergotoxine, ergotamine, guanidine, methylguanidine and dimethylguanidine all elevated blood pressure to some degree in sufficient dosage, but simultaneously constricted the auricular vessels and always diminished peripheral blood flow. Unheated 5% saline extracts of normal rabbit kidney usually reduced, and only occasionally elevated, blood pressure; peripheral blood flow, however, always decreased during the pressor response.

Similar 5% saline extracts of normal rabbit kidney, treated by heating to between 55° and 56° C., followed by filtration at or near 55° C., had no depressor action but always raised blood pressure conspicuously without decreasing skin temperature during any part of the pressor response. This property of elevating blood pressure without reducing peripheral blood flow depended upon a protein-like substance which could not pass an ultrafilter, remained in solution up to 56° C., was precipitated or destroyed by heating to 65° C., and could be precipitated by ammonium sulphate, resembling in these respects the substance named "renin" by Tigerstedt and Bergmann.

Of all the pressor substances studied, these specially heated kidney extracts, and the protein-like material precipitated from such extracts, were the only ones which elevated blood pressure without decreasing peripheral blood flow, a relationship which is also characteristic of certain forms of human hypertension.

The Action of Chemical Substances on the Cerebral Circulation. C. F. SCHMIDT and J. P. HENDRIX (Laboratory of Pharmacology, University of Pennsylvania). In anesthetized cats intracranial (parietal cortex) and extracranial (tongue or mylohyoid muscle) blood flow was measured simultaneously by thermocouples. Drugs were injected into the ipsilateral common carotid.

Cutting the ipsilateral cervical sympathetic nerve usually increased extracranial blood flow, never intracranial flow. Weak stimulation of the cephalic end always reduced extracranial flow, seldom intracranial flow. *Vasodilators* varied greatly in their relative effectiveness on intracranial and extracranial blood flow: CO_2 (inhaled) increased intracranial and decreased extracranial, histamine increased extracranial and decreased intracranial, nitroglycerine increased both about equally, while cholines increased extracranial markedly, intracranial slightly, and caffeine was relatively ineffective on both; ether (inhaled) increased intracranial flow and decreased extracranial until vasomotor depression occurred. *Vasoconstrictors* (adrenalin, ephedrine, pituitrin, pitressin) decreased extracranial flow markedly, intracranial not at all. Only ergotamine showed an inconstant constrictor action upon intracranial vessels, and this only in large dosage.

In rabbits, intracranial blood flow was restricted to one internal carotid, by ligating the opposite internal carotid and the basilar arteries, and measured by a thermostromuhr on the common carotid. Simultaneously flow was measured in the parietal cortex by a thermocouple. Stimulation of the ipsilateral cervical sympathetic usually reduced total and parietal flows, the latter somewhat less. Occasionally reduction was sufficient to produce symptoms of cerebral anemia. In one experiment, fatal spasm of cerebral vessels resulted, relieved temporarily by nitroglycerine. CO_2 increased total and parietal flow; quantitative measurements indicate that the increase in total flow may exceed 100%. The effects of drugs were essentially the same on both flows and similar to those seen in cats.

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1938

ORIGINAL ARTICLES.

THE NATURAL HISTORY OF CHRONIC HEPATITIS (CIRRHOSIS OF THE LIVER).

By Arthur L. Bloomfield, M.D.,
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(From the Department of Medicine, Stanford University School of Medicine.)

Our interest in the evolution of chronic hepatitis (cirrhosis of the liver) was aroused some years ago by the case of a middle aged man in whom at operation following a large gastric hemorrhage there was found not the expected gastric ulcer but a small shrunken cirrhotic liver. The patient had been a vigorous man apparently in perfect health until a few months before his death. He did not use alcohol. The cause of the cirrhosis was obscure until it was brought out that 11 years previously he had had an attack of so-called catarrhal jaundice. The thought seemed not unreasonable that slowly progressive changes in the liver followed this bout of acute hepatitis, in spite of apparent complete recovery, and that when these changes had finally become extreme terminal evidences of cirrhosis rapidly appeared. Stimulated by this observation we realized that little attention had been paid in the literature to the precursors of the later stages of chronic hepatitis (cirrhosis). Addis' studies of Bright's disease have clearly shown[1] the frequency of long latent periods, following the initial insult to the kidneys when for years the subject may appear entirely well, even though proper studies of urinary sediment and of renal function demonstrate a relentlessly progressive lesion which finally results in renal insufficiency and clinical uremia. It is known that such latent periods may be punctuated by clinical exacerbations, and also that the initial stage can be acute and clinically violent (acute nephritis) or entirely below the threshold of clinical observation. We developed a similar concept of hepatitis[3] on a more or less hypothetical basis and the present purpose is to reinforce the views previously outlined by an analysis of cases which we have actually observed. Most of our conclusions have been reached in the past by others,[2,5,11] but piecemeal, and scattered through the literature; it would seem useful to bring all this material together in "a round unvarnished tale."

Material. During the past 5 years the diagnosis of chronic hepatitis or cirrhosis was made in approximately 100 cases in our clinic. After discarding those in which the diagnosis seemed in doubt and those which were insufficiently observed there remained some 50 well documented records. In each instance some or all of the classical findings were present: hepatic facies, spider angiomata, fetor hepaticus, jaundice, ascites, and induration of liver and spleen. Measurements of blood bilirubin, morphological studies of the blood, and so on were adequate. In many cases the patients were followed over periods of years and finally came to autopsy. We found it impossible clinically to subdivide the cases into various types or diseases; they all conformed in the end to the familiar picture variously spoken of as atrophic, portal, alcoholic or Laennec's cirrhosis. Among 42 patients with advanced cirrhosis 36 gave the usual history of marked alcoholism; otherwise the etiology was entirely obscure.

The Relation of Advanced Hepatitis (Cirrhosis) to an Antecedent Acute Hepatitis. Forty-one patients who were observed in an obviously advanced stage of cirrhosis were thoroughly cross examined as to a possible attack of acute hepatitis in past years. Special emphasis was placed on history of jaundice. The results of this inquiry were strikingly barren. In only 4 cases was there a definite story of an ancient jaundice; in 3 others there was a doubtful history and in 2 others a statement too vague to be trustworthy. Inasmuch as a real attack of icterus is usually remembered and patients err on the side of giving false histories of jaundice (when they have merely been sallow or pale), it seems safe to conclude that acute hepatitis is rarely the precursor of or the initial stage of what later develops into advanced cirrhosis. The conclusion seems of particular interest since it has been pointed out[2,5,11,12] that many people who have had an attack of simple jaundice (acute catarrhal, acute infections) continue for some time—perhaps for years—to show evidence of impaired hepatic function in the form of an elevated blood bilirubin content. It may be that acute simple jaundice really comprises a group of different diseases; at any rate it is impossible at present to differentiate those patients in whom recovery takes place from the few who will progress to extreme lesions. The situation is further complicated by the fact that alcoholism, so important in cirrhosis, bears no special relation to simple acute jaundice.

The following are brief abstracts of the 4 cases in which there was definite history of old jaundice:

CASE 1. T. M. (No. A-53249), a 47-year-old markedly alcoholic Spaniard, entered the hospital in 1935 complaining of nosebleed and "yellow eyes." He stated that in 1908 he had been "very yellow all over" and was sick enough to be in bed for a month. Examination now showed slight icterus with a hard smooth liver down to the umbilicus. No definite ascites. Icterus index 24. Indirect Van den Bergh 4.75 U. Wassermann test negative. Spinal fluid negative. Red blood cells 4.9 M., hemoglobin 99% Sahli, white blood cells 4350.

Impression: Chronic hepatitis. Possible relation of old jaundice to present condition.

CASE 2.—A. McCl. (No. 98890), a 51-year-old markedly alcoholic American, was seen in March, 1937. He gave an unequivocal history of an attack of jaundice 12 years ago but was then well until 1 year ago, when jaundice recurred with general failure and swelling of the abdomen. He had been tapped several times. Examination: A very thin man with big belly full of fluid, hepatic facies, spider angiomata, and icterus. Red blood cells 4.2 M., Hemoglobin 70% Sahli, white blood cells 6300. Icteric index 16, Van den Bergh 4.0 U., Takata-Ara +, Rose Bengal 50% of normal function. Plasma protein 6.25 gm. %. Slight fever.

Impression: It seems highly probable that this disease began with acute hepatitis 12 years ago, with slowly progressive latent changes until clinical symptoms of advanced cirrhosis finally appeared.

CASE 3.—J. G. (No. A-42909), a 39-year-old markedly alcoholic American, entered the hospital in March, 1934, with complaint of gas pains. There was a definite story of jaundice 8 years previously. He says his skin and eyes were intensely yellow for at least a week. After recovery he felt perfectly well and in December, 1932, applied for life insurance; he was told by the examiner that he had cirrhosis, probably on the basis of a palpable liver. A few months later jaundice appeared and his abdomen became full. Examination: Icterus, hepatic facies, hard liver 2 fb. below costal margin, moderate ascites. Red blood cells 3.2 M., hemoglobin 62% Sahli, white blood cells 9800. Icteric index 42, Van den Bergh 10 U., Wassermann test negative. He was observed over a period of a year during which his condition remained essentially unchanged.

Impression.: Acute hepatitis 8 years ago followed by slowly progressive latent changes in liver; diagnosis of cirrhosis made in latent stage during life insurance examination; finally obvious clinical cirrhosis.

CASE 4.—H. P. (No. 129019), a markedly alcoholic Mexican woman, aged 41, entered the hospital in 1935 for "bruise spots" on her body. She gave a definite story of being very yellow all over in 1918 when the doctor said her liver was enlarged and advised operation. In 1924 she was in the Stanford skin clinic for a sebaceous cyst. No general examination was made but there were no complaints to suggest cirrhosis then. On entry in April, 1935, she was slightly icteric and there were large spider angiomata. A hard edge was felt 3 cm. below C. M. and the spleen was palpable. No ascites. Red blood cells 3.9 M., hemoglobin 13.6 gm. %, C. I. 1.0+, M. C. V 101 cu. μ. Van den Bergh 3 U. November, 1935, she became drowsy and ran low fever. Vomited large quantities of blood. Ascites developed. Icteric index 40 U. Died November 14, 1935. *Autopsy:* Extreme cirrhotic process. Dense fibrous strands separating small groups of liver cells. It was the impression that this was the end stage of a very sluggish old process. In this case it seems certain that a lesion existed for a much longer time than the 8 months during which she had symptoms. It seems probable that the attack of hepatitis in 1918 was the initial event followed by a long latent progressive stage.

The course of Cases 1 to 4 is shown graphically in Fig. 1.

Another case illustrates the fact that advanced cirrhosis may follow an old acute hepatitis which never produced any clinical symptoms.

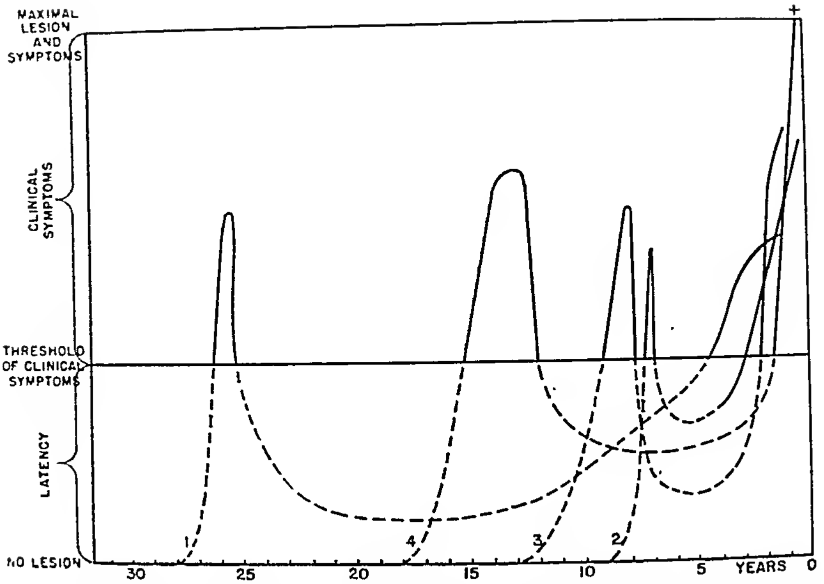

FIG. 1.—Diagram of clinical course of Cases 1 to 4. In this and the following charts that part of the course shown in broken lines is probable but not actually observed.

CASE 5.—N. D. (No. A–19088), a 48-year-old American laborer, had used alcohol to excess. He entered the hospital in January, 1932, with the story that he had always been perfectly well. He had never been jaundiced, nor confined to bed with any acute illness. For several months prior to entry he had failed generally and had lost 20 pounds. One week ago he noticed swelling of the belly. On examination he presented a full-blown picture of advanced cirrhosis with slight icterus, hepatic facies, spider angiomata, palpable hard liver and ascites. Icteric index 20, Van den Bergh 3 U., Wassermann test negative. After a few days he became stuporous and died in coma. At autopsy, there was found indisputable evidence of an ancient acute hepatitis in the form of a so-called healed acute yellow atrophy. The liver weighed 880 gm., was brownish and shrunken with irregular yellow nodules. The brown areas showed scar tissue and bile ducts with no parenchymal cells, and functioning liver tissue was represented only by the scattered yellow nodules. How long ago the attack of acute hepatitis occurred is obscure, but it undoubtedly led in the end to the picture of advanced cirrhosis with liver insufficiency.

This case corresponds quite accurately with those described by Pratt and Stengel,[9] by Goodpasture[13] and others as healed acute yellow atrophy leading to toxic cirrhosis (Mallory). The clinical picture at the end was however in no way distinguishable from the ordinary terminal stage of Laennec's cirrhosis.

The etiology of all the above cases is uncertain; whether alcohol alone is responsible seems problematical.

Evidence that Latent Hepatitis May Exist for Long Periods. The statistics presented in the previous section show that it is a rare event for the changes which eventuate in progressive cirrhosis to be initiated by a clinical attack of acute hepatitis. In fully 80 to 90%

of the present series the first clinical symptoms were those associated with a process already far advanced. It seems probable, then, that in cirrhosis of the Laennec's type there is usually no violent destruction of the liver but a lesion which from the start may be sluggishly progressive over a long period of time. That this is in fact the case we were able to demonstrate in 2 cases in which definite evidences of latent hepatitis were detected 8 and 11 years respectively before clinical symptoms appeared. In this connection we define the latent stage as that in which, if there are any abnormal findings, elevation of blood bilirubin and induration of liver or spleen exist without any departure from health. The presence of toxic symptoms, visible jaundice, ascites, or hematemesis remove the case from the latent to the clinically active group.

Case 6.—A. J. (No. 182627), a 40-year-old markedly alcoholic Italian, was first seen in 1928 with the complaint of kernels in the neck. A lymph node showed chronic adenitis which seems of no further significance in the case. During the general physical examination a firm liver edge was felt 2 cm. below the costal margin, and the edge of the spleen was palpable. No visible jaundice. Blood count normal. For the next 8 years he was clinically well and active, and it was only by deliberate search that the evidences of a gradually progressive but latent cirrhosis were detected:

June, 1930, liver 3 to 4 cm. below C. M., smooth and firm; R. B. C. 4.5 M., Hb. 82%, Icteric index 20 U., Van den Bergh 2.5 U. April, 1931, liver unchanged. May, 1933, liver unchanged; spleen felt 4 cm. below C. M.; R. B. C. 4.7 M., Hb. 90%, M. C. V. of red cells 98 cu. μ; average R. B. C. diam. 7.8 μ; icteric index 13 U. Van den Bergh 1.25 units. September, 1933, icteric index 24 U.; Van den Bergh 4.5 U. December, 1933, icteric index 24 U.; R. B. C. 4.6 M., Hb. 93%, M. V. C. 105 cu. μ. March, 1934, icteric index 13 U. June, 1934, icteric index 16 U. September, 1934, liver and spleen as before; icteric index 15; feels perfectly well. June, 1935, condition unchanged; R. B. C. 4.8 M., Hb. 95%, M. C. V. 95 cu. μ, Van den Bergh 0.75 U. November, 1936. Entered hospital with complaint of swelling of abdomen and legs for 4 months. During this time had become weak and short of breath. There had been some blood in the stools. On examination, he was slightly undernourished and there was fetor hepaticus. The belly was distended with fluid. Liver 2 cm. and spleen 15 cm. below costal margin. R. B. C. 3.9 M., Hb. 75%, W. B. C. 5000. Icteric index 24 U. Van den Bergh 7.5 U. Rose Bengal 26% of normal function. Slight elevation of temperature. He was tapped several times but rapidly became toxic and died on February 3, 1937. *Autopsy* showed very advanced cirrhosis of the portal type.

This case is reported somewhat at length, but it is of unusual interest. Over 8 years we observed, after accidental discovery, induration of liver and spleen with slight hyperbilirubinemia in a man clinically well. A pathological increase in red blood cell size was definite 3 years before symptoms developed. Finally, there was rapid onset of clinical signs of advanced cirrhosis and death in coma within 8 months.

Case 7.—E. C. (No. 67081), a 70-year-old Italian who denied the use of alcohol, was first seen in the clinic in 1918 for a mild nephritis and hypertension. At that time a firm liver was felt 3 cm. below C. M. and the spleen was readily palpable. The red blood count was normal but there was a constant leukopenia of 2000 to 3000. There were no clinical symptoms of hepatitis but in 1926, 8 years later, he was in the hospital for a slight cerebral accident. The liver and spleen were as before and now there was a slight hyperchromic anemia with R. B. C. 3.6 M., Hb. 73%, C. I. 1+, W. B. C. 2100. It was not until February, 1929, 11 years after he was first seen, that clinical symptoms of liver disease appeared and he entered because of swollen abdomen and weakness of several months' duration. After tapping, a very hard liver was felt in the epigastrium. R. B. C. 4.8 M., Hb. 82%, W. B. C. 6000, icteric index only 8 U., and Van den Bergh 0.25 U. There were repeated taps but he died of general failure in April, 1929.

It seems clear that a gradually progressive hepatitis had existed for a great many years.

In both Cases 6 and 7 the recognition of latent hepatitis was made possible by the fortuitous chance of the patients' coming under observation for complaints unrelated to the liver disease. It seems probable that signs of insidious hepatic lesions could be detected in many people who eventually appear with advanced cirrhosis were there an opportunity of making physical examinations during antecedent years. The course of Cases 6 and 7 is shown in Fig. 2.

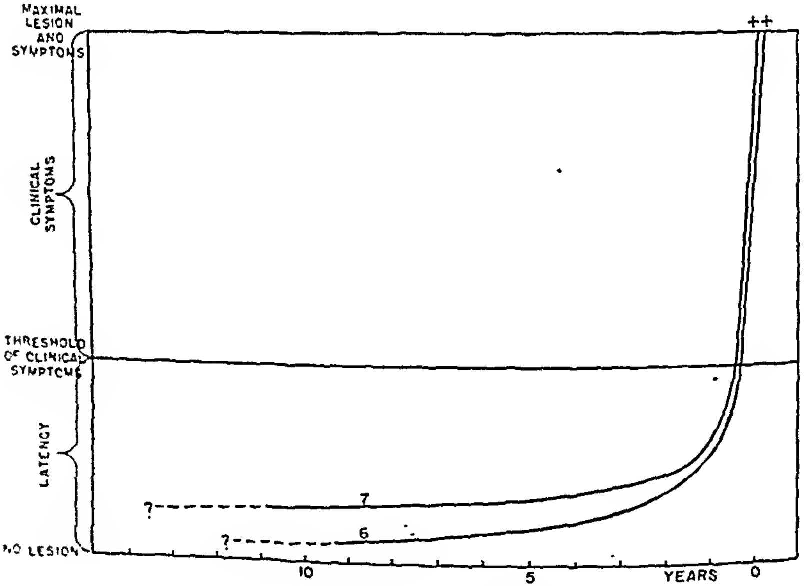

FIG. 2.—Clinical course of Cases 6 and 7.

Acute Exacerbations During the Course of Chronic Hepatitis and the Difficulty of Differentiation from Initial Acute Attacks. The etiology of acute hepatitis is obscure except in those cases which follow certain drugs or poisons, and in those occurring in epidemic form, probably the result of infectious agents (epidemic jaundice, Weil's disease, yellow fever). The cause of the common variety of sporadic hepatitis seen in civil practice is still a mystery. Pathological material is scanty but there is good reason to believe that one may be dealing with a group and not with a single disease. Certainly there are a variety of clinical types. The classical "catarrhal jaundice" is usually a mild disease showing little more than the presence of icterus and perhaps a palpable liver. Recovery is the rule and even though a slight hyperbilirubinemia may persist for a considerable period this type of disease rarely, as we pointed out above, goes on to progressive chronic hepatitis. At the other end of the scale are those instances of obscure necrosis of liver cells—acute yellow atrophy—usually fatal in a few weeks. But cases of every degree of severity between these two extremes seem to occur and recent papers have dealt with acute hepatitis associated with ascites and evidences of great "toxemia" which may heal or at least be followed by clinical recovery.[4,8] It is this type of disorder which we wish now to discuss in its relations to hepatitis as a whole—both acute and chronic. Of particular interest is the distinction between fresh initial attacks and acute exacerbations of chronic hepatitis. The cases described below show that it is often impossible to make a clinical differentiation.

I. Cases Probably or Certainly Representing Initial Attacks of Hepatitis.

Clinical picture indistinguishable from advanced chronic hepatitis, but in fact an initial attack of acute hepatitis running its entire course to death in coma in 4 months.

Case 8.—C. P. (No. A-44622), a moderately alcoholic Italian woman aged 36, had always been well. In April, 1934, she was thoroughly examined in connection with the diagnosis of a mild skin lesion. There was nothing then to suggest liver disease. Hb. 75%, R. B. C. 4.1 M., W. B. C. 6900. She returned to the clinic 8 months later (December 12, 1934), with a story of increasing swelling of abdomen and jaundice for 3 months. She was now obviously icteric and the liver was enlarged to the level of the umbilicus, smooth and slightly tender. The spleen was not felt. There was high irregular fever. R. B. C. 2.3 M., Hb. 8.2 gm. %, C. I. 1.0+, M. C. V. 115 cu. μ, icteric index 50 U., Van den Bergh 5 U., W. B. C. 33,000, P. M. N. 87%. December 26, 1934, exploratory laparotomy. There was a large quantity of ascitic fluid, the gall bladder was normal, the spleen was firm and twice normal size. The liver was large and had a stippled appearance. Biopsy showed subacute cirrhosis—not the picture of acute yellow atrophy. Cultures from bile and abdominal fluid were sterile. She continued to run high fever after operation, jaundice persisted, ascites reaccumulated, there was progressive macrocytic anemia. She gradually went into coma and died January 12, 4 months after initial symptoms.

Discussion. The story of alcoholism and the clinical features were typical of an advanced chronic cirrhosis. The negative examination 4 to 5 months before onset of symptoms and the histology of the liver make it clear however that one was really dealing with a rapidly progressive initial attack of hepatitis. The etiology of this type of liver disease, clinically quite different from the usual variety of "catarrhal jaundice" and anatomically not acute yellow atrophy, is obscure. The case corresponds to those described by Jones and Minot,[7] and others.

Acute hepatitis with jaundice and ascites undistinguishable at first from advanced cirrhosis. Biopsy—subacute yellow atrophy. Clinical recovery. Question of residual damage.

Case 9.—I. W. (No. A-66297), an American woman, aged 58, who denied use of alcohol, was well until September 20, 1936, when she was taken with abdominal soreness and weakness and later nausea and jaundice. On entrance into hospital, October 12, she appeared ill, there was definite icterus, and a deeply placed mass in R. U. Q., probably liver. October 21 exploratory laparotomy showed the liver to be small, grayish, scarred and irregular. Biopsy showed an acute hepatitis with diffuse necrosis of liver cells. After operation there was increase of nausea, intense jaundice with icteric index 200 U., Van den Bergh 60 U., and ascites. She was tapped twice. R. B. C. 3.9 M., Hb. 80% Sahli, C. I. 1.0+, W. B. C. 7000, M. C. V. 93 cu. Average diam. of R. B. C. 8.8 μ, Wassermann test negative. She seemed desperately ill but made an unexpected recovery and left the hospital on November 24, only 6 weeks after entry. At that time she was still slightly jaundiced but there was no reaccumulation of fluid. In May, 1937, she returned for study. She was apparently perfectly well. Physical examination was negative except that tip of spleen was palpable. R. B. C. 4.2 M., Hb. 84% Sahli, icteric index 7 U., Van den Bergh 0.5 U., M. C. V. 88 cu. μ., Rose Bengal showed very slight delay in abstraction of dye from blood; estimated function 70% of normal.

Discussion. This case is of interest as the third instance in our series of hepatitis with jaundice and ascites with recovery. It seems practically certain that this was an initial attack of hepatitis, now in a healed or latent stage. Further observation is necessary to see whether there will be progression to chronic hepatitis.

Acute hepatitis probably initial, but possibly exacerbation of an old process.

Case 10.—R. S. (54895), a 55-year-old German who denied use of alcohol, entered hospital on June 24, 1935, with the complaint of jaundice and nausea for 5 weeks. He was thin, markedly icteric, the liver was enlarged and there was ascites. R. B. C. 3.5 M., Hb. 70% Sahli, M. V. C. 134 cu. μ, icteric index 125 U., Van den Bergh 25 U. Exploratory laparotomy 3.L fluid, gall bladder normal. Biopsy of liver showed atrophy of periportal cells with increase in connective tissue and proliferation and dilation of bile capillaries. He gradually improved and by July 31 seemed definitely on the road to recovery. Icteric index down to 25 U., M. C. V. of R. B. C. still 112 cu. μ. On August 1 a seminal vesiculotomy was done for some old trouble and he died 2 days later of postoperative complications. *Autopsy:* Spleen weighed 350 gm. Liver cut with increased resistance. There was central necrosis with increase in peripheral connective tissue which was infiltrated with round cells. Anatomical diagnosis: subacute hepatitis.

Discussion. It is extremely difficult to decide whether the hepatitis is recent or old but the histology of the liver suggests a fairly recent process. It seems probable therefore that one is dealing with an initial attack which was, clinically at least, subsiding when an ill advised operation upset his balance.

II. Instances of Probable or Certain Acute Clinical Exacerbations of a Chronic Hepatitis.

Old "alcoholic" hepatitis with acute exacerbation of symptoms practically indistinguishable from an initial attack.

Case 11.—G. P. (No. A–58592), a 57-year-old German-American liquor salesman, had drunk heavily for 30 years, but his general health had been very good. Three weeks before entrance on November 14, 1935, he noticed rapid swelling of the abdomen and jaundice. On examination he was obese, there was light icterus and an immense collection of abdominal fluid. After tapping, a hard liver edge was felt 2 cm. below costal margin. R. B. C. 3.9 M., Hb. 70%, M. V. C. 101 cu. μ, average diameter 8.1 μ. Wassermann test negative. Icteric index 34 U., Van den Bergh 3.75 U., Rose Bengal 20% of normal function. Takata-Ara +, blood urea 63 mg. %. He was extremely ill and stuporous from entry to January, 1936, and was tapped frequently. Gradual improvement then set in. He was tapped repeatedly for the next few months but in March, 1937, no tap had been necessary for 19 weeks and only 3 L. were obtained. No reaccumulation 3 weeks later (June, 1937). Icteric index 8 U., Van den Bergh 1 U. Feels perfectly well—firm liver edge just palpable.

Discussion. It seems probable that one is dealing here with an acute exacerbation of an old hepatitis, but the differentiation from an initial attack is practically impossible.

Terminal exacerbation of old chronic hepatitis clinically indistinguishable from an initial attack.

Case 12.—A. H. (No. A–71212), a 59-year-old American woman, had used alcohol heavily for years. Recently she had eaten very little and had practically lived on gin and tea. There was nothing in the past history otherwise to suggest liver disease. Present illness began 3 weeks before entry on May 13, 1937, with weakness, nausea, and vomiting. Jaundice for 1 week. Examination showed an obese sick woman, markedly jaundiced, the skin covered with "bruise spots." Ascites was present and a very hard irregular liver was felt. R. B. C. 2.9 M., Hb. 72% Sahli, C. I. 1.2, W. B. C. 8800, M. C. V. 112 cu. μ., platelets 107,000. Bleeding time indefinitely prolonged. Coagulation time 9 minutes. Icteric index 81 U., Van den Bergh 25 U. No autodigestion of blood clot. Rose Bengal 20% of normal function. Wassermann test negative. She failed rapidly and died in coma May 26, about a month after onset of symptoms. Autopsy showed an extreme cirrhosis of a very chronic type. The changes were undoubtedly of great duration. There were no evidences of acute liver degeneration.

Discussion. Clinically the case is indistinguishable from those instances of initial hepatitis reported above, but here one is undoubtedly dealing with a terminal clinical exacerbation of an old chronic process.

III. Cases in Which it Was Impossible to Decide Between Initial Acute Hepatitis or Acute Exacerbation of an Old Hepatitis.

Acute hepatic coma with jaundice and ascites in a chronic alcoholic. Remarkable recovery. Question whether it is a case of initial acute hepatitis or an acute exacerbation during the course of chronic hepatitis.

Case 13.—S. F. (No. A–43139), a markedly alcoholic American woman, aged 44, was first seen in the clinic in March, 1934, for tonsillectomy. Examination at that time showed no evidence of liver disease although there was no specific note on the abdomen. She was perfectly well until October, 1934, when she was brought to the hospital in coma. Relatives gave the story that she had been on numerous alcoholic debauches but was not ill until 2 weeks before entry when she was taken in the night with epigastric distress, nausea and vomiting. On examination, she presented the typical picture of hepatic coma: jaundice, fetor hepaticus, large spider angiomata and ascites. She was tapped twice for 650 cc. and 950 cc. There was moderate fever. R. B. C. 2.8 M., Hb. 11.3 gm. %, C. I. 1.2, M. C. V. 109 cu. μ, average R. B. C. diameter 7.9 μ, Wassermann test negative, icteric index 30, Van den Bergh 3 U., blood urea 217 mg. %. She appeared moribund but under parenteral glucose and saline rapidly improved and left the hospital 18 days after entry practically well. The blood urea had fallen to 25 mg.% and icteric index to 10 U., and the blood count was R. B. C. 4.4 M., Hb. 14.9 gm., M. C. V. 96 cu. μ. There was no reaccumulation of ascitic fluid and the liver edge was felt just below C. M.

She returned 2 years later in October, 1936, for study. She had been perfectly well and looked the picture of health. The spider angiomata had disappeared. No ascites. Liver and spleen not felt. R. B. C. 4.7 M., Hb. 78% Sahli, M. C. V. 92 cu. μ., icteric index 4 U., Van den Bergh 0.5 U., Rose Bengal test showed delayed removal of dye from blood giving an estimated hepatic function of 42%.

Discussion. With the history of alcoholism and the clinical findings it seemed quite certain when she was first seen that one was dealing with advanced cirrhosis and terminal hepatic coma. The extraordinary recovery with continued good health raises the question of whether she did not have an initial acute hepatitis. The Rose Bengal test suggests a residual liver damage, but there is no other evidence of hepatitis now. Of interest are the very high blood urea without signs of nephritis, the disappearance of large spider angiomata as she recovered (a phenomenon which we have never seen before) and the development of transient macrocytic anemia. This last feature has been noted by Rosenberg[10] and others in similar cases.

Jaundice and ascites in an alcoholic. Question of acute exacerbation in the course of chronic hepatitis or initial attack.

CASE 14. M. S. (No. 167400), an American laborer, aged 28, had used alcohol freely. He had always been well until 3 weeks ago when he had abdominal discomfort and noticed distention of abdomen and jaundice. On entry, September 1, 1927, there were dilated venules over face, spider angiomata, jaundice, ascites and a firm liver extending a hand's breadth below C. M. There was slight elevation of temperature. R. B. C. 4.7 M., Hb. 83% Sahli. Wassermann test negative. Icteric index 96 U., Van den Bergh 12.5 U. He was tapped and improved rapidly. On discharge, September 22, there was no reaccumulation of fluid, jaundice had disappeared (Van den Bergh 0.5 U.), the temperature was normal and the liver was definitely smaller.

Discussion. Unfortunately it was not possible to follow this patient. In view of the alcoholic history the question comes up whether this was an exacerbation of a latent hepatitis or an initial acute attack with recovery. Recovery from hepatitis with ascites is said to be excessively rare and McCabe and Hart[8] were able to collect only 10 instances from the literature. This patient, however, is only one of a number of such cases in the present series.

Question of initial attack of hepatitis or acute exacerbation of chronic cirrhosis. Clinical recovery with residual signs of latent hepatitis.

Case 15.—A. A. (No. A–61907), a 42-year-old American fireman, gave a history of extreme alcoholism. He had frequently been suspended from the fire department for drunkenness. He entered the hospital April 10, 1936, for an injury to his ankle 1 week before, unaware of jaundice. On examination, there was typical alcoholic facies, spider angiomata on chest, a smooth liver 4 cm. below C. M. and marked icterus. There was moderate fever and the jaundice became more intense. On April 15 the icteric index was 270 U. and the Van den Bergh 70 U. He rapidly developed a severe macrocytic anemia with R. B. C. 1.8 M. and Hb. 44% Sahli. Average diameter of R. B. C. 8.7 μ and M. C. V. 125 cu. μ, W. B. C. 17,000. Wassermann test negative. Bleeding time 9 minutes. Under rest, parenteral fluids and glucose and liver extract there was remarkable improvement and he left the hospital on May 26 feeling perfectly well. At that time icteric index was only 6 U., R. B. C. 3.4 M., Hb. 68%, W. B. C. normal. No fever, The liver was still palpable. On June 23 he went back to work. April, 1937, in hospital for study. Appears perfectly well. Spider angiomata still present. Liver and spleen not felt. R. B. C. 4.4 M., Hb. 92%, C. I. 1.0+, W. B. C. 6400, icteric index 8 U. Van den Bergh 1 U., M. C. V. 91 cu. μ. Rose Bengal test shows definite delay in removal of dye—liver function estimated as 65% of normal.

Discussion. It is impossible to say whether this was an initial attack of hepatitis or an acute exacerbation of a chronic cirrhosis. At any rate, in spite of clinical recovery there remains definite evidence of latent chronic hepatitis.

This group of cases seems of particular importance in an analysis of the life history of hepatitis. One should emphasize the short length of time necessary for the full blown clinical picture of cirrhosis to develop following an initial attack of hepatitis, the fact that the first clinical evidences of a long standing hepatitis may be those of a terminal "toxemia" which leads to death in a few weeks; and finally how all but impossible it often is to distinguish between initial attacks of hepatitis and clinical exacerbations of an old latent cirrhosis. This leads to a discussion of repeated acute exacerbations and remissions during the course of chronic hepatitis. Cases similar to ours have been well described by Fiessinger, Albot and Thiebaut.[6]

Case 16.—B. B. (No. 181668), a 53-year-old markedly alcoholic Italian, always well previously, stated that 4 years ago he was in another hospital for swollen abdomen and legs. He was tapped several times, but after some months the swelling disappeared and he was perfectly well and working for 3½ years. For the past few weeks there had been loss of weight, indigestion, and recently jaundice and swelling of the abdomen. Examination (November 7, 1928) showed a picture of advanced cirrhosis—icterus, spider angiomata and ascites. R. B. C. 3.0 M., Hb. 61%, C. I. 1.0+, Wassermann test negative. Icteric index 30 U., Van den Bergh 4.5 U. By November 26, 1929, he was much improved, abdominal fluid did not reaccumulate and he felt well but still had slight icterus and anemia. He did very well until January 25, 1930—an interval of a year—when he was brought in after rapid onset of semicoma. He was quite jaundiced but there was no ascites. Liver not felt but spleen palpable. Under treatment he improved slightly but died in April, 1930, in typical hepatic coma. *Autopsy* showed typical changes of advanced cirrhosis.

Discussion. Here there were clearly several clinical exacerbations and remissions. The course is best visualized by the diagram (Fig. 3).

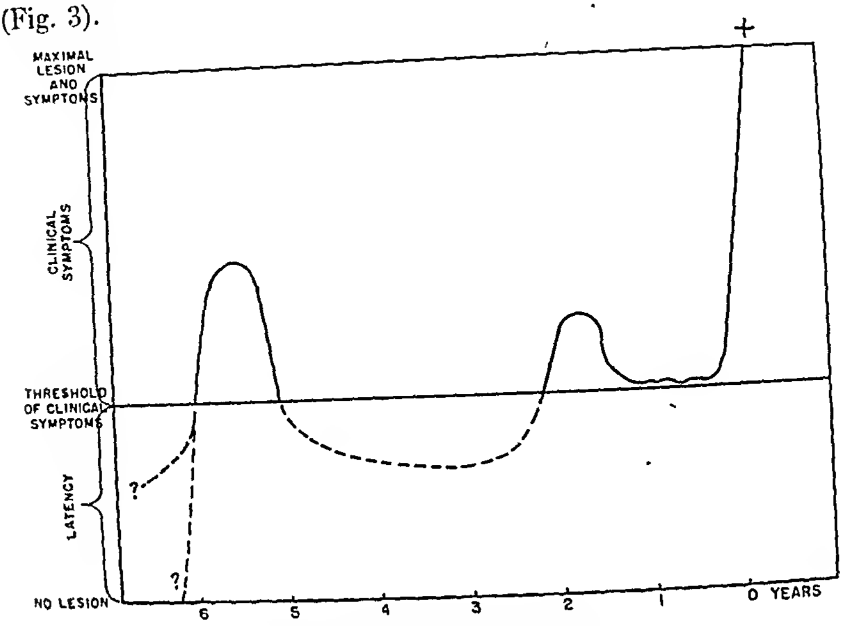

Fig. 3.—Clinical course of Case 16.

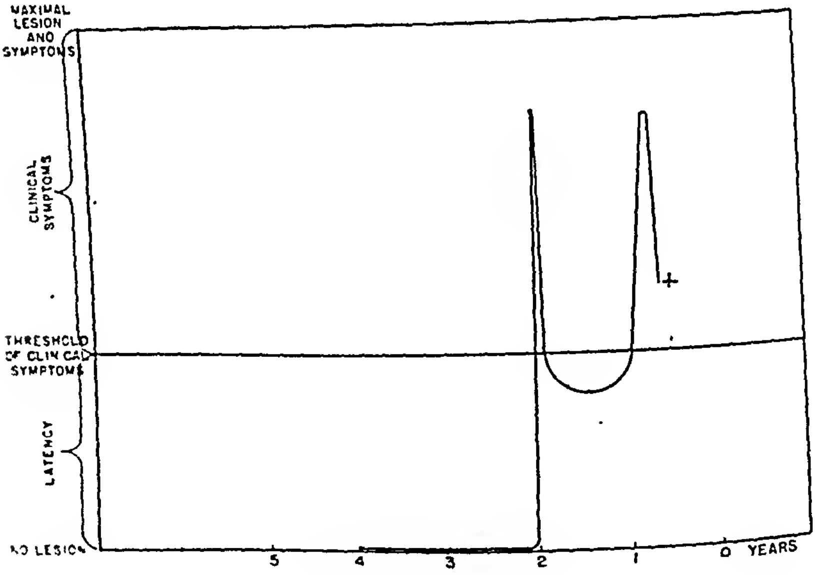

Fig. 4.—Clinical course of Case 17.

Case 17.—C. D. (No. A-23476), a 59-year-old markedly alcoholic American, was first seen in May, 1932, for injury to his hand. At that time there was no suggestion of liver disease and neither liver nor spleen was felt. Wassermann test negative. Blood count normal. He was well until February, 1934, when he entered the hospital for epigastric pain of a few days' duration. He looked ill, there was high fever, light icterus and a tender liver a few cm. below C. M. W. B. C. 25,000, icteric index 31 U. He improved quickly and within 3 weeks was discharged with normal temperature and leukocyte count, and icteric index of 6 U. Gastro-intestinal Roentgen rays were negative and liver was no longer palpable. He was entirely well for a year until January, 1935, when he returned with complaint of epigastric pain and fever for 3 days. Exploratory laparotomy, January 22, showed the liver to be scarred, nodular and brick red. Biopsy was done. Gall bladder normal. He improved rapidly and by January 31 seemed on the road to recovery when there was sudden exitus from pulmonary embolus. *Autopsy*—subacute diffuse portal cirrhosis.

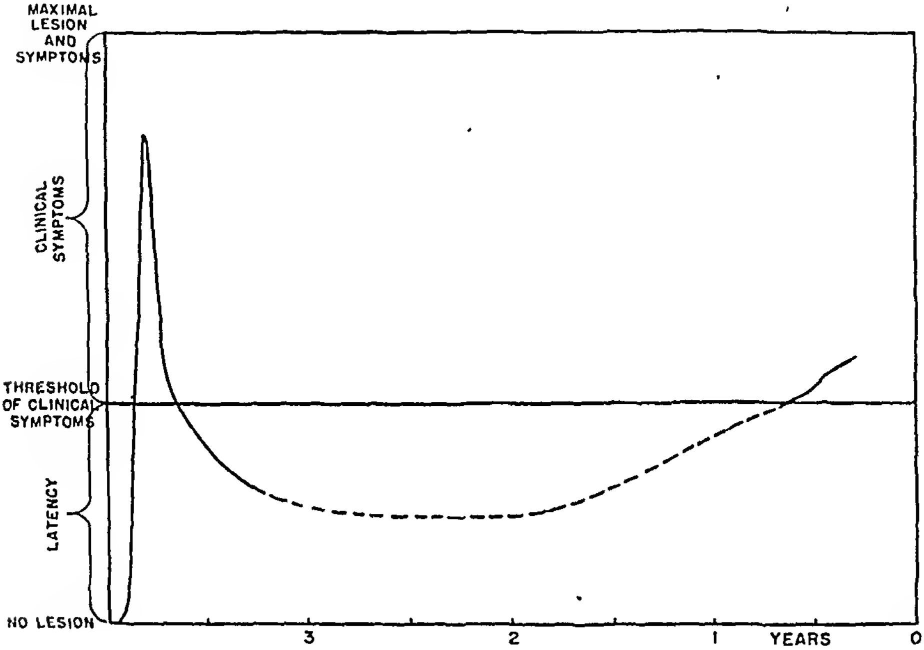

FIG. 5.—Clinical course of Case 18.

Discussion. The course of events is shown graphically in the diagram (Fig. 4). It seems clear that the episode in 1934 was an initial acute attack of hepatitis followed by apparent recovery (but probably actually a latent state with residual damage) until the second acute exacerbation a year later, from which again he seemed to be recovering. The histologic findings make it clear that the disease was of longer duration than the last acute attack, in which he died in less than a month from onset of symptoms.

CASE 18.—H. P. (No. A–39763), a moderately alcoholic American, aged 51, stated that he had been jaundiced for 1 week in 1927 but otherwise had been well. In November, 1933, he entered the hospital with the story of an acute illness of 5 weeks' duration featured by chills, abdominal pain, nausea, vomiting, and recently jaundice. On examination, there was marked icterus and a firm smooth liver was felt 3 cm. below C. M. R. B. C. 3.9 M., Hb. 13.4 gm. %, C. I. 1.0, W. B. C. 5700, M. C. V. 101 cu. μ., Wassermann test negative. Icteric index 111 U., Van den Bergh 25 U. Slight fever, not above 38° C. He improved gradually and by February, 1934, he felt well. Icteric index was 7.5 U. Liver edge still palpable. He remained subjectively perfectly well for 3 years until May, 1937, when he returned with the story of swelling of legs and enlargement of abdomen for 2 months. On examination, he was a little under weight and there were small spider angiomata. Liver no longer palpable, soft edema of legs. Plasma protein 6.2 gm. %. Icteric index 19 U., Van den Bergh 5 U., R. B. C. 3.9 M., M. C. V. 89 cu. μ.

Discussion. The story of jaundice in 1927, while not definite suggests an attack of hepatitis then. After a remission of 6 years he had, in 1933, an exacerbation under our observation with clinical recovery for 3 years and finally a third recurrence of obvious clinical disease. The situation is summarized in the diagram (Fig. 5).

In addition to such clear cut instances of exacerbation and remission many illustrations could be given of patients whose course varies from better to worse without any extreme fluctuation, and for no assignable reason.

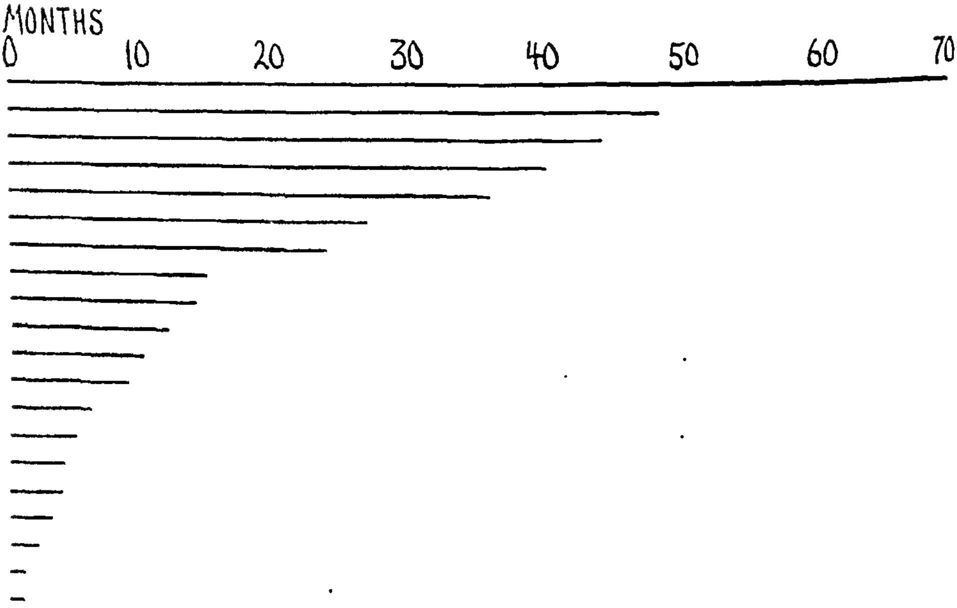

FIG. 6.—Duration of life after onset of symptoms in fatal cases of cirrhosis. Each line is a different patient.

Terminal Stage. There remain for discussion certain clinical aspects of the terminal stage. To simplify the analysis we have segregated all of our cases in which after a latent period of unknown duration death occurred in the first accession of clinical symptoms and autopsy showed advanced cirrhosis. The causes of death were the familiar ones—bleeding, intercurrent infection, postoperative accidents and hepatic coma. The duration of life after onset of clinical symptoms is shown graphically in Fig. 6. The striking finding is that in this series of 20 cases, 45% of the patients died within a year and 40% within 6 months. This shows to what an extent latent chronic hepatitis may progress before clinical trouble becomes evident.

Discussion. In the preceding pages we have attempted to build up a composite picture of the life history of those obscure instances of hepatitis which are still of unknown etiology. Cases due to assignable cause (aside from the possible influence of alcohol), such as poisons, drugs and known infections, are not included in this discussion which must necessarily then be largely clinical and empirical. The relation of the type of anatomic lesion to the course of the disease will be analyzed in another paper. None of our observations is entirely novel but it seems worth while to synthesize information about hepatitis, which for the most part is scattered in the literature or has not been sufficiently emphasized.

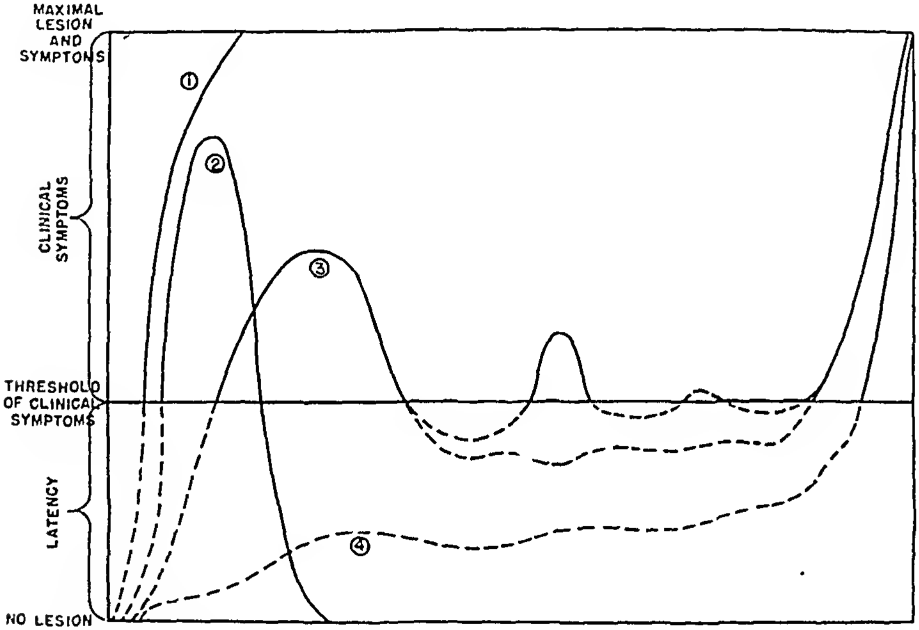

Fig. 7.—Variations in the course of hepatitis. (1) Acute hepatitis progressing rapidly to death. (2) Acute hepatitis with recovery. (3) Acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis. (4) Hepatitis latent from the start until advanced liver insufficiency supervenes

The initial stage of hepatitis may be clinically acute and promptly fatal. This group includes not only cases of so-called acute yellow atrophy but also instances of a less violently destructive process. An equally acute onset may be followed by complete clinical recovery and probably by healing of the lesion, although it is hard to prove that latent anatomical changes are not present. The possibility of such latent changes, which may gradually progress over many years until clinical hepatic insufficiency supervenes, is shown by those instances of late cirrhosis in which a story of acute hepatitis years ago can be elicited. As illustrated by some of the cases reported above, recognizable but clinically latent disease can be detected and actually observed over long periods. In our series, it was striking that the initial stage of the common variety of advanced hepatitis (Laennec's cirrhosis) was usually latent; in some 90% of the cases there never was any early clinical episode but both lesion and symptoms were latent until the final crash of hepatic insufficiency. The latent periods may be punctured by clinical exacerbations which again subside into latency, and thus such a cycle may be repeated a number of times before the patient dies. The main possibilities are shown graphically in Fig. 7, and the analogy to the course of glomerular nephritis as analyzed by Addis is brought out.

Conclusions. 1. Cirrhosis of the liver is usually the terminal stage of a long disease which runs most of its early course without clinical symptoms.

2. In the present series, the disease was initiated by an acute clinical attack of hepatitis in only 4 of 41 cases (10+ %). In most of the patients the onset was entirely obscure.

3. Acute clinical exacerbations may occur during the course of a progressive latent hepatitis to be followed by further periods of latency.

4. Such acute exacerbations are often indistinguishable from initial attacks of acute hepatitis.

5. Acute hepatitis may run a rapid course with the development in a few weeks or months of the clinical picture usually associated with advanced cirrhosis. Clinical recovery may take place in these cases.

6. In the case of patients with prolonged chronic hepatitis (cirrhosis) who die in their first clinical exacerbation the course is usually brief; in about one-half the cases not over 1 year from onset of symptoms to death.

7. A composite picture of the life history of acute and chronic hepatitis of obscure origin is presented by means of diagrams and illustrative cases.

NOTE. Throughout this paper the term acute hepatitis is used in a non-committa sense insofar as the exact lesions and their etiology are not entirely clear. Acute hepatitis, however, seems a better term than catarrhal jaundice, simple jaundice or infectious jaundice and preserves the analogy with obscure disease of other organs such as nephritis, arthritis, etc.

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THE EFFECT OF BENZEDRINE SULPHATE ON THE BOWEL AND UTERUS.

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Benzedrine (benzyl methyl carbinamine), a volatile vasoconstrictor allied chemically to ephedrine, was introduced primarily for topical application to the nose and throat in the treatment of congested mucosal surfaces.[2] Benzedrine sulphate, a salt of the base, is soluble in water and has been found active when given by mouth in doses ranging between 5 and 20 mg., although larger doses have been used under controlled circumstances. The conception that benzedrine sulphate might prove advantageous in gastro-intestinal spasm and colic has apparently arisen by analogy with the effect of epinephrine. Sympathetic relaxation of the bowel by epinephrine is a well-known pharmacologic reaction and benzedrine is a sympathomimetic substance. Myerson and Ritvo[5] and Myerson, Loman and Dameshek[6] have proposed that benzedrine sulphate is of value in relieving gastro-intestinal spasm, basing their conclusion on clinical observations aided in some instances by Roentgen ray visualization in man. On the other hand, Peoples and Guttmann[7] could find no symptomatic evidence of any effect of benzedrine sulphate on the gastro-intestinal tract of man. Detrick, Millikan, Modern and Thienes[3] found that benzedrine sulphate actually contracted isolated segments of small intestine of rabbits and guinea-pigs. Also in rats, receiving large doses of benzedrine sulphate, Ehrich and Krumbhaar[4] frequently found postmortem markedly contracted segments of small intestine. In the face of this conflicting evidence, it was considered advisable to repeat the experiments of Detrick *et al.*[3] and in addition to study the effect of benzedrine sulphate on another organ containing smooth muscle, the uterus. The results obtained amply confirm the results of Detrick, Millikan, Modern and Thienes.[3] While this does not necessarily mean that benzedrine sulphate will also contract the human intestine, it is obvious that further work should be done on man.

Method. Short segments of small intestine were taken from freshly killed rabbits and the uterine horns from freshly killed virgin guinea-pigs. Rhythmic contractions of bowel were found much better if the small intestine was moderately filled with warm Locke's solution before removing the segments. The bowel segments and uterine horns were set up in Locke's solution in a side arm test tube connected with a U-thistle tube and surrounded by a water bath maintained at 35° to 37° C. according to the Magnus technique and rhythmic contractions were recorded kymographically. After satisfactory records of normal contractions had been obtained, benzedrine sulphate, ephedrine hydrochloride and epinephrine hydrochloride were added to the warm Locke's solution about the bowel or uterus to a concentration of 0.01 to 0.001%. The record obtained was analyzed to determine the effect of these sympathomimetic substances on the tonus (base line) and rate and strength of rhythmic contractions of the smooth muscle.

TABLE 1.—THE EFFECT OF BENZEDRINE SULPHATE, EPHEDRINE HYDROCHLORIDE AND EPINEPHRINE HYDROCHLORIDE ON ISOLATED SEGMENTS OF SMALL INTESTINE OF RABBITS AND THE VIRGIN GUINEA-PIG UTERUS.

Value.	Benzedrine.			Ephedrine.			Epinephrine.		
		Contractions.			Contractions.			Contractions.	
	Tonus.	Rate.	Strength.	Tonus.	Rate.	Strength.	Tonus.	Rate.	Strength.
	Small Intestine.								
Mean (% change) . . .	+49	−5	+14	+22	+2	+94	−65	−13	−25
Standard deviation . .	32	13	30	40	16	78	19	30	29
% cases like change in mean	100	71	59	65	59	77	100	71	71
	Uterus.								
Mean (% change) . .	+52	+21	+66	+64	+24	+60	−94	−100	−100
Standard deviation . .	22	36	101	22	26	61	9	0	0
% cases like change in mean	94	55	55	100	80	80	100	100	100

Results. (Table 1.) All changes in the record were calculated in per cent of the original before application of the salts studied. The averages of these changes are given in Table 1. To illustrate the variation in the changes, the standard deviation of the means have been included and to indicate the consistency of the reaction, the percentage of experiments in which the changes observed were in the same direction as that of the mean has also been determined. It is usually recognized statistically that a mean change in order to be significant should be at least twice its standard deviation. In a number of instances shown in Table 1, the standard deviation was greater than one-half of the mean and yet nearly 100% of the experiments showed a change in the same direction. For example, the tonus of 100% of bowel segments was increased by benzedrine, the average increase was 49% and the standard deviation of the average increase was 32%. In this instance the increase in tonus was obviously significant, but the calculated mean was not typical of the group; in other words, there was considerable variation in the *extent* of the increase in tonus. In all instances the mean values were those of 15 to 20 experiments.

Benzedrine invariably produced a prolonged contraction of the longitudinal muscle of the small intestine and of the smooth muscle of the uterus. Since this change raised the base line from which rhythmic contractions started, it was recorded as an increase in tonus. The rate and strength of rhythmic contractions from this elevated base line were not significantly different after application of the benzedrine sulphate. The predominant feature of the action of benzedrine was thus a prolonged, spastic type of contraction of the smooth muscle of these organs.

The action of ephedrine was essentially similar to that of benzedrine though not quite as consistent. Epinephrine, on the other hand, relaxed the smooth muscle and inhibited practically all rhythmic contractions. The difference was a striking one and demonstrated clearly that benzedrine and ephedrine have not the same effect as epinephrine on the smooth muscle of the gut and uterus in these 2 species. In this respect, benzedrine and ephedrine differ from meta-synephrine, another related sympathomimetic substance, which relaxes the uterus and bowel like epinephrine.[1]

Previous cocainization of the surviving bowel segments if anything increased the inhibition by epinephrine; but the stimulation produced by benzedrine and ephedrine was less after cocaine hydrochloride. In this set of 17 experiments, the average rise in tonus produced by benzedrine previous to cocaine was 51% and after cocaine it was 37%; corresponding values for ephedrine were +40% and +15% and for epinephrine −80% and −100% respectively. The contractions produced by benzedrine and ephedrine were thus not increased by cocainization, suggesting that their action was not entirely, if at all, on the nerve endings of the motor sympathetic system.

This conclusion was confirmed by further experiments on the reaction following ergotamine tartrate on isolated bowel segments. There was no consistent change in the effect of benzedrine on rabbit small intestine after ergotamine, the average effect being a slightly decreased stimulation both by benzedrine and ephedrine. Epinephrine was slightly more depressant after ergotamine. It is obvious therefore that benzedrine does not act upon the motor sympathetic nerve endings in the rabbit small intestine.

Nor was the effect related to the parasympathetic system. Previous abolition of parasympathetic influence by atropine had no consistent effect on the action of either benzedrine or ephedrine on the surviving bowel segments of rabbits. From these experiments and in the light of present conceptions of sympathetic and parasympathetic reactions, it may be concluded that benzedrine in the concentrations used in this study contracts the smooth muscle of the intestine of rabbits and of the uterus of guinea-pigs by a direct action upon the muscle fibers.

In one experiment, benzedrine contracted a rabbit uterus with a pregnancy of about 2 weeks' duration. In another experiment, the urinary bladder of a guinea-pig was contracted by all 3 of benzedrine, ephedrine and epinephrine, while a spleen from a guinea-pig failed to respond to any of the 3 substances.

Summary. Benzedrine sulphate (concentrations of 0.01 to 0.001%) was found to produce a prolonged, spastic contraction of strips of the smooth muscle of the uterus of virgin guinea-pigs and isolated segments of small intestine of rabbits. From experiments following ergotamine, cocaine and atropine, it was concluded that this action was directly upon the smooth muscle fibers.

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SYMPTOMATIC TREATMENT OF CHRONIC ENCEPHALITIS WITH BENZEDRINE SULPHATE.

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This paper deals with the clinical results observed in 20 patients with chronic encephalitis having a Parkinsonian syndrome treated with benzedrine sulphate (benzylmethylcarbinamine), 18 of whom have been receiving the drug by mouth for a period of from 6 to 12 months.

Solomon and Prinzmetal[3] have employed the drug in postencephalitic Parkinsonism and reported the results obtained in 28 cases with classical symptoms. Improvement was noted in 53% when benzedrine sulphate was used alone and in 93% when it was given in conjunction with stramonium or scopolamine. Of this group, 22 were able to do more work; 20 observed a decrease in their muscular rigidity; 19 said they felt stronger; 7 observed a decrease or disappearance of their tremor, 9 noticed no change in tremor and the other 12 did not have tremor. In 8 patients with oculogyric crisis, the attacks were eliminated in 6 and greatly diminished in the other 2 when benzedrine was given in addition to scopolamine and stramonium. The drug was found of no value in arteriosclerotic Parkinsonism.

In considering the rationale for its use in these conditions, it may be pointed out that in Parkinsonism we see definite evidence of autonomic dysfunction based on hypothalmic lesions. The drugs of greatest value in postencephalitic Parkinsonism are stramonium, atropine and hyoscine, all of which are said to exert their activity by a sedative action on the parasympathetic side of the autonomic nervous system, although a central brain stem effect must also be considered. The disturbed sleep mechanism so often observed in this disease can probably be accounted for on the same anatomic basis. It has been shown experimentally by Dikshit[1] that injection of acetylocholine, a parasympathetic stimulant, into the ventricles

TABLE 1.—EFFECT OF BENZEDRINE SULPHATE ON PARKINSONIAN SYNDROME IN 20 CASES.

Case. Sex. Age	Outstanding symptoms.	Duration of symptoms in years.	Previous medication continued.	Benzedrine sulphate daily, amount (mg.).	Blood pressure before and after treatment.	Pulse rate before and after treatment.	Weight before and after treatment.	Results of treatment.
1 M 60	Salivation, tremor rt. hand, myoclonus of eyelids	6	Hyoscine Tr. stramonium	50 10 mos.	B 110/70 A 124/70	B 72 A 64	B 145 A 145	Eye sympt. disappeared, more alert and cheerful.
2 M 33	Oculogyric crises, rigidity, slight tremors	8	Hyoscine Tr. stramonium	40 7 mos.	B 85/60 A 112/68	B 105 A 105	B 123 A 128	No subjective or objective improvement.
3 M 49	Generalized rigidity, tonic elevation left shoulder, "grunting"	9	Tr. stramonium	40 12 mos.	B 110/80 A 110/80	B 112 A 96	B 153 A 157	Less rigidity, "grunting" decreased, more alert and cheerful.
4 F 21	Rigidity rt. leg, oculogyric crises, irritability	6	Tr. stramonium	25 6 mos.	B 90/50 A 120/56	B 90 A 84	B 122 A 126	Oculogyric crises controlled more cheerful, less irritable, less rigidity.
5 M 49	Marked rigidity and tremors, salivation, myoclonus eyelids	7	Tr. stramonium	40 12 mos.	B 120/90 A 120/90	B 120 A 112	B 135 A 143	Myoclonus eyelids less marked, salivation diminished, more cheerful and alert.
6 F 35	Rigidity, oculogyric crises, headache, drowsiness, salivation	5	Hyoscine	40 9 mos.	B 88/60 A 88/60	B 72 A 80	B 209 A 209	Fewer and less severe oculogyric crises.
7 F 36	Rigidity, tremors, depression	4	Tr. stramonium	50 10 mos.	B 90/60 A 110/60	B 80 A 80	B 146 A 145	Improvement in mood: not maintained.
8 M 47	Rigidity, tremors	3	Hyoscine	15 1 wk.	B 100/60	B 88	..	Tremors aggravated, refused to continue medication.
9 M 29	Rigidity, tremors, depression	8	Tr. stramonium	30 7 mos.	B 88/60 A 110/78	B 78 A 94	B 125 A 121	Much more cheerful and alert, more energy, less rigidity.
10 F 30	Salivation, tremors, rigidity	8	Atropine	30 8 mos.	B 98/60 A 92/60	B 100 A 110	B 85 A 88	Much more active, alert and cheerful, less rigidity.
11 M 50	Obesity, somnolence, marked tremors	6	Tr. stramonium	20–40 12 mos.	B 120/85 A 120/85	B 80 A 80	B 283 A 267	Somnolence controlled, more alert and cheerful.
12 M 52	Salivation, rigidity, oculogyric crises	7	Tr. stramonium	40 11 mos.	B 125/90 A 100/78	B 128 A 80	B 114 A 114	Oculogyric crises less frequent and severe, less salivation, more energy.
13 F 29	Rigidity, tremors, fatigue, oculogyric crises	5	Tr. stramonium	25 9 mos.	B 100/76 A 110/90	B 112 A 108	B 137 A 126	Fewer oculogyric crises, less tremor, more energy, more cheerful.
14 M 21	Slight rigidity, irritability, periods of excitement	2	Atropine	15 6 mos.	B 110/80 A 110/80	B 100 A 94	B 113 A 110	Distinct improvement in mood, no periods of excitement in 6 mos.
15 M 37	Rigidity, weakness, mental clouding	4	Atropine	20 9 mos.	B 130/72 A 130/78	B 120 A 118	B 142 A 144	More alert and cheerful, more energy.
16 M 38	Salivation, tremors, rigidity	7	Tr. stramonium	50 5 mos. 25 7 mos.	B 80/? A 90/70	B 110 A 110	B 107 A 113	More alert and cheerful, much more energy.
17 M 47	Weakness, rigidity, salivation, drowsiness	1	Atropine	90 8 mos. 30 7 mos.	B 110/70 A 120/90	B 82 A 82	B 120 A 112	Salivation controlled, distinctly more alert and cheerful.
18 M 44	Tremors, rigidity, somnolence	5	Hyoscine	20 1 wk.	.....	..	..	Tremors aggravated, subjectively much worse, refused to continue medication.
19 F 28	Rigidity, weakness, tremors, depression	5	Atropine	15 7 mos.	B 100/70 A 116/70	B 78 A 104	B 112 A 112	Slightly more cheerful, otherwise no change.
20 F 26	Severe oculogyric crises, headache, rigidity, tremors	4	Tr. stramonium	50 7 mos.	B 100/75 A 98/62	B 115 A 100	B 162 A 162	Oculogyric crises shorter and less severe, tremors slightly aggravated.

or hypothalamic region in rats produces a condition resembling normal sleep. Benzedrine, a sympathetic stimulant, or more accurately an adrenalergic drug, exerts its effect in part by enhancing the activity of the drugs, which are parasympathetic sedatives. The Ziskinds[4] in a recent article call attention to the fact that phenobarbital in ordinary therapeutic doses aggravates certain types of rigidity, probably because of its action on the brain stem. They also raise the question as to whether or not physiologic antidotes for the barbiturates may not have a salutary effect in the treatment of the plastic type of rigidity. Benzedrine can be considered such an antidote. Nathanson,[2] studying the effect of benzedrine on a large group of normal individuals, found that it has a definite stimulating action on the higher centers of the central nervous system in most persons besides producing a peripheral response.

Since May, 1936, benzedrine sulphate has been administered to a group of patients with chronic epidemic encephalitis in the Neurologic Out Patient Department of this hospital. Twenty have been treated and followed for a sufficiently long period to justify a report of the clinical observations. These patients were studied from the standpoint of the effect of the drug on specific symptoms, blood pressure, pulse rate and weight. Pertinent data relative to the cases treated is summarized in the accompanying table.

Comment. The blood pressures and pulse rates indicated in the table represent basic levels before and after treatment and not merely isolated readings. Unusually high or low readings were not taken as representative of the true state of the cardiovascular mechanism but evaluated in each individual case.

It was found that many of these patients tend to have a low blood pressure accompanied by a rapid pulse rate which may be only a manifestation of their general state of debilitation, although autonomic imbalance probably accounts for this in part. Those individuals with an initial low blood pressure which increased in response to therapy, as a rule, showed an accompanying decrease in pulse rate and were the patients who acquired greater energy and strength.

Discussion. Of the 20 patients studied, 15 (75%) have shown definite sustained improvement which must be attributed to benzedrine alone, since no change was made in the medical régime which was previously being carried out. In 1 other case some sustained improvement has been noted, but in view of an alteration in the previous medication this cannot be attributed entirely to the benzedrine therapy. One case was better at first but improvement has not been maintained. One patient has not been helped and 2 claim that their symptoms were definitely aggravated by the drug and refused to continue taking it. The improvement noted has not always been the same in every case. Oculogyric crises were controlled or diminished in frequency and severity in 5 of 6 cases. In 2 patients with myoclonus of the eyelids the symptom was greatly benefited. Thirteen patients have manifested a distinct improvement in mood, have become more cheerful and state that they have more energy. There has been a lessening of rigidity and tremor in a number of patients but this has not been constant and is difficult to evaluate clinically. In 4 cases salivation has become less troublesome. Systolic blood pressure has been raised 10 points or more in 9 patients, has not varied more than 10 points in 8 and was reduced more than 10 points in 1 instance. The remaining 2 patients did not take the drug long enough to provide reliable data. An initial low blood pressure was found in the majority of these patients, 11 having a systolic pressure below 100. The maximum sustained pressure rise in any case was 30 degrees systolic and 20 degrees diastolic. The patients whose blood pressure has been raised materially are in most instances the ones whose pressure was originally low.

The pulse rate was lowered more than 5 beats per minute in 8 patients, did not vary more than 5 points in 6, and was increased in 4 cases. Reliable data were not available in 2. Since the maximum effect of the drug, as manifested by changes in the blood pressure and pulse rate, is said to occur from 10 minutes to 1½ hours after administration and is continued for several hours, the recorded readings were made near the height of the reaction since they were made between 10.30 and 12 in the morning and the largest daily dose of the drug was directed to be taken at 8 A.M.

There was a gain in weight of 1 pound or more in 7 patients, weight remained unchanged in 5, there was weight loss in 6, and no data in 2. The loss in weight, with 1 exception, was not troublesome and occurred in patients who were originally somewhat overweight. The patient who lost the most weight was the man who took 90 mg. of benzedrine daily for 5 months. The weight loss ceased when the dose was decreased to 30 mg. daily but the symptomatic improvement has been maintained. There is much to suggest that doses in excess of 40 to 50 mg. daily are not required to obtain maximum benefits. In this patient and several others there appeared to be an accumulative action or increasing sensitivity to the drug as indicated by the side effects since it became necessary to lower the dosage to avoid sleeplessness and gastro-intestinal symptoms in the form of vomiting. In no instance were the side effects sufficiently troublesome to necessitate discontinuing the administration of benzedrine. Two patients complained of burning on urination with some difficulty in starting the stream but these symptoms cleared spontaneously in 1 case and disappeared on withdrawal of the drug for 2 days in the other without recurrence. However, a medical colleague reports that after taking 30 mg. of benzedrine during a period of stress and strain with physical exhaustion he experienced an adrenalergic reaction characterized by tachycardia, hypertension (pressure rise 25 mm., systolic), dilated pupils, insomnia, nausea and vomiting, and suppression of urine for an 18-hour period. His condition was such as to require hospitalization.

The results of the studies made so far have been encouraging and suggest further investigations. Although a large percentage of these patients have been benefited, the improvement can hardly be other than symptomatic and it is questionable how long it will be maintained. It is not possible at this time to evaluate how much improvement has been based on psychogenic factors, but an attempt will be made to determine this by the use of a placebo in a group of controls. Patients repeatedly reported an aggravation of symptoms when they were without the drug for a few days. In addition, studies of the effect of the drug in this series of patients may help to throw light on its possible efficacy in other types of illness.

Conclusions. 1. Of 20 patients with chronic encephalitis having a Parkinsonian syndrome who received benzedrine sulphate for a period of from 6 to 12 months, 75% have shown definite symptomatic improvement.

2. The symptoms beneficially affected were not the same in every case, but collectively included lessening of rigidity, tremor, salivation and oculogyric crisis. In addition, there was improvement in mood and an increase of strength and energy.

3. Benzedrine enhances the effect of stramonium, atropine and hyoscine and is best used in conjunction with these drugs in the treatment of postencephalitic Parkinsonism.

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THE EXPERIMENTAL PATHOLOGY OF ERGOTISM.

WITH REFERENCE TO SOME NEWER ERGOT DERIVATIVES.*

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INTEREST in ergot continues to follow identification of the several alkaloids, 12 thus far, particularly since the isolation of ergonovine†

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* This investigation was aided by a grant from John Wyeth and Brother, Inc., Ph[illegible]

† Within a few months of one another in 1935 the following ergot alkaloids were isolated: ergometrine (Dudley and Moir), ergostetrine (Thompson), ergobasine [illegible] and ergotocine (Davis et al.). These were proven later to be identical and the name "ergonovine" was adopted by the Council of Pharmacy and Chemistry of the American Medical Association.

which is the principle responsible for the prompt and vigorous contraction of uterine musculature. It appears, from the pharmacologic standpoint, that the ergot alkaloids can be divided into two general groups, represented by ergotoxine and ergonovine; the former acts mainly on smooth muscle of blood-vessels and has a delayed and relatively weak but protracted oxytocic effect, the latter invoking a rapid but more evanescent uterine response. The clinical implications of ergot fractionation are based on that fundamental difference, particularly in the treatment of migraine (ergotamine tartrate, a member of the ergotoxine group) and in the *status post partum* (ergonovine). Recently ergonovine has assumed importance in migraine therapy as well.[8]

Soon after the isolation of ergonovine (1935) several commercial preparations appeared which were standardized for their content of the alkaloid. One of these, ergoklonin (Wyeth), containing 1 mg. of ergonovine per cc. and freed of the bulk of the ergotoxine group, was subjected to clinical trial in the obstetrical wards of the Philadelphia General Hospital[12] and has been adopted for routine use, supplanting fluid extract of ergot. The experimental work reported here was begun at that time, primarily to determine the safety of the preparation.

Conflicting reports concerning the production of gangrene in the cock's comb with ergonovine have been published. Brown and Dale[1] noted a quite normal comb after injecting 65 mg. intramuscularly over a period of 5 days, although each injection was followed by deep cyanosis and the usual general symptoms. Davis *et al.*,[2] however, injected 6 cocks with 0.5 mg. of "ergotocin" twice daily for 24 days and stated, "One bird developed gangrene of the comb in 8 days, another in 5 days, and still another had a similar lesion 15 days after the completion of the injections." The melting point of the alkaloid used in the latter experiment was slightly different from that of Brown and Dale, due possibly to impurity, thus accounting perhaps for the varied result. An editorial comment[6] warned of the possibility of gangrene from ergonovine, but I know of no such instance resulting from its clinical administration. Ergotamine tartrate has produced gangrene in patients with sepsis or liver disease;[5,9,13] Lennox,[8] however, has found it safe in a large group of cases being treated for migraine, some over a period of almost 5 years.

Regarding the mechanism of ergot gangrene it was not until 1935 that a thorough investigation was published. Lewis and Gelfand,[7] studying "The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning," using ergotoxine ethanesulphonate, reported: "Gangrene of the hen's comb can be produced regularly by day to day injections of 10 mg. ergotoxine into the breast muscles. A constriction of the arteries, which is unrelieved by relaxing vasoconstrictor tone or by local warming, is thereby maintained and, though a little flow of blood continues, serious nutritional changes occur by the end of a few days. The endothelium of the vessels suffers, plasma is lost and stasis occurs in the capillaries, vascular clotting follows in central vessels, which are by this time dilated, and necrosis is determined. All these changes can be produced within a few days by mechanically impeding the blood flow to the comb. Vascular spasm in ergot poisoning does not arrest the circulation, and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels described; these are responsible for the arrest of blood flow, which in turn results in death of the tissues."

Drugs Employed.* In order to evaluate any possibility of ergotism through administration of ergoklonin, 3 concentrations of the drug were used, normal (as prepared for clinical use), twice normal and 4 times normal, the stronger solutions being concentrated *in vacuo*. The pure alkaloid, ergonovine (0.5 mg./cc.), and fluid extract of ergot, U. S. P., were employed for comparison.

Standardization of Animals. Ergotoxine ethanesulphonate in a 1% aqueous solution of tartaric acid was prepared in the strength of 0.5 mg./cc. Of this, 0.15 mg./kg. body weight was given each of the animals (white Leghorn cocks acceptable for U. S. P. ergot assay) intramuscularly. Comb response to this "bluing dose" was recorded as 0, 1, 2, 3, individually for each third, anteriorly to posteriorly, no animal being used which had a reaction less than 011, nor more than 223, as observed 15 minutes after injection. This eliminated birds which were either unusually tolerant or hypersensitive to ergot.

Procedure. Cocks were housed under uniform conditions, mostly caged singly, but a few in pairs, with adequate maintenance feeding. The several groups received intramuscular injections of the following drugs, the dose being twice the volume of the "ergotoxine bluing dose" except in Group 4 which is doubled:

Group	Drug.	No. of animals.	Dose (cc./kg.)	Ergonovine equivalent. (mg./kg.)
1	Fluid extract of ergot (twice daily)	11	0.6	
2	Ergoklonin (normal concentration) (twice daily)	10	0.6	0.06
3	Ergoklonin (concentrated 2×) (twice daily)	9	0.6	0.12
4	Ergoklonin (concentrated 4×) (twice daily)	5	1.2	0.48
5	Ergonovine (twice daily)	2	0.6	0.30
6	Ergonovine (4 times daily)	3	0.6	0.30

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* Supplied by Wyeth, the ergonovine was crystallized and the solution prepared by Dr. M. R. Thompson, Professor of Pharmacology, University of Maryland.

PLATE I.

A. Normal cocks: White Leghorn cocks acceptable for U. S. P. ergot assay. B, [illegible]. Reactions 1 2 3, 15 minutes after intramuscular injection of ergotoxine ethanesulphonate (0.15 mg./kg. body weight). C. Fluid extract of ergot: Marked atrophy and gangrene produced by intramuscular injection of 1.02 cc. [illegible] twice daily for 15 days (No. 115). D. Fluid extract of ergot: Marked atrophy and gangrene [illegible] of digits 6 and 7 produced by intramuscular injection of [illegible] twice daily for 15 days (No. 131). E. Ergonovine: Deep cyanosis 1 hour [illegible] cock had received 0.7 mg. intramuscularly 4 times daily during the [illegible] days (No. 170). F. Ergonovine. Same animal 4 hours after the reaction [illegible] very slight residual cyanosis (No. 170).

PLATE I

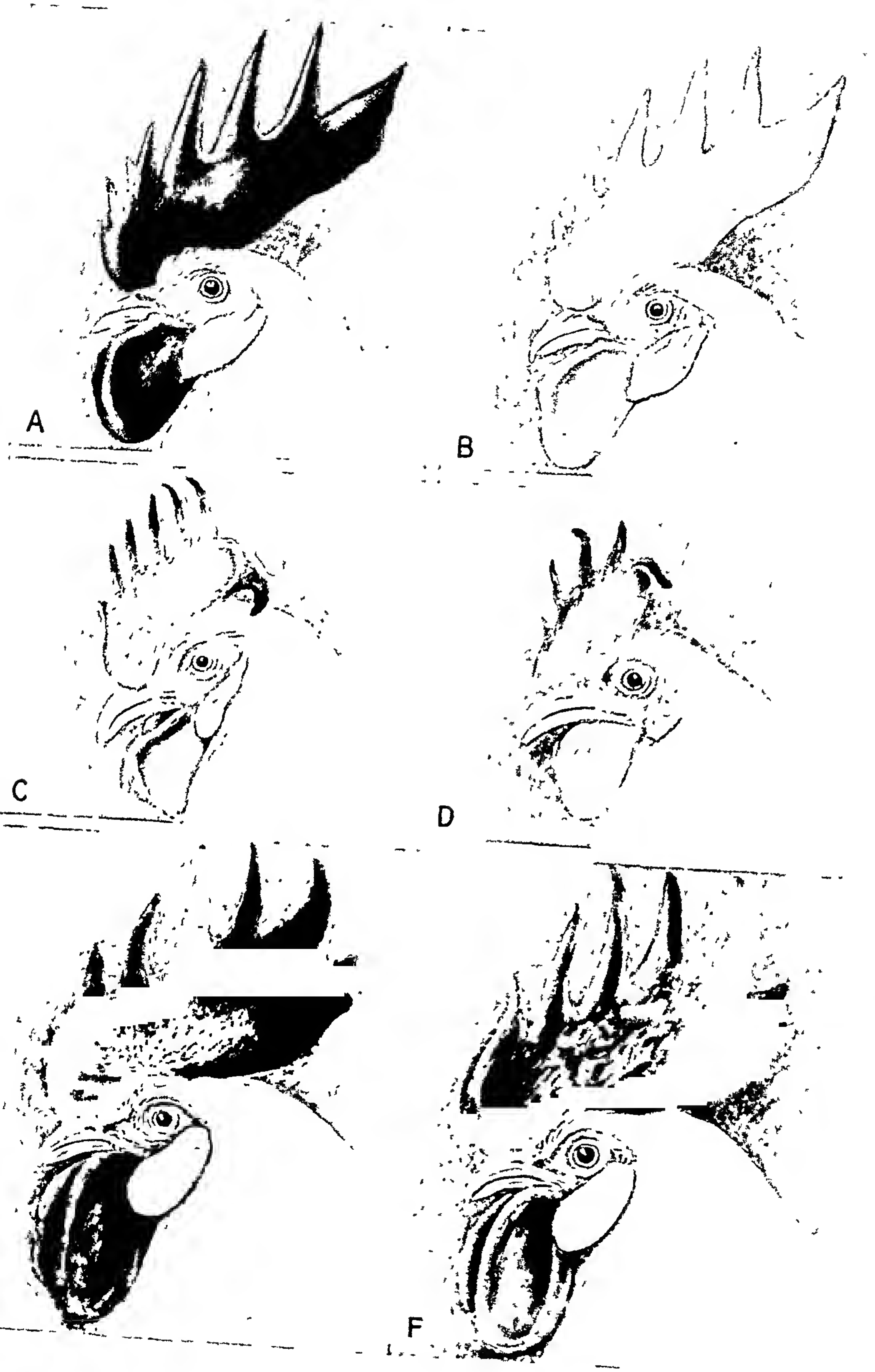
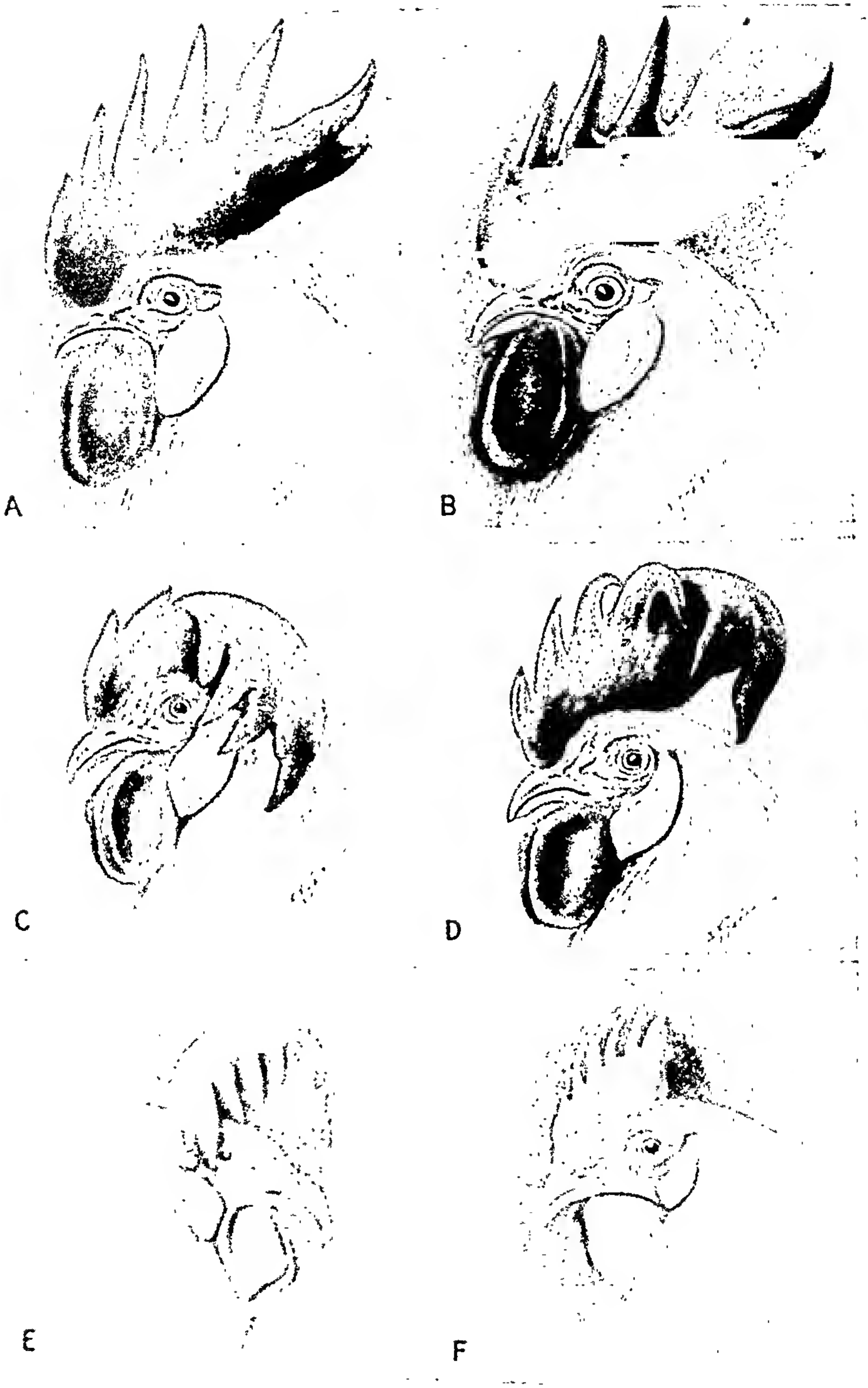


PLATE II



Consecutive injections were made in clockwise rotation through the 4 quadrants of the breast. Gangrene was produced in the combs of 5 cocks by application of a heavy elastic band. Sixteen birds were sacrificed for control.

Injections were continued for 30 days in all groups except the first; the fluid extract produced such massive sloughs that there was little or no absorption after the 14th day and the last animal was killed on the 25th.

Longitudinal and transverse sections were taken through digitations 6 and 7 of the comb and from brain (in some), aorta, heart, lungs (in some), spleen, kidney, testis (in some), stomach, liver and breast muscle, for histologic examination.

Results. General Status of the Animals. 1. *Fluid extract of ergot:* There was marked loss of weight, the animals rapidly becoming extremely emaciated. Breast muscle was necrotic and the majority showed ulceration; 54% of this group died, one 5 days after injections were begun.

2. *Ergoklonin (normal concentration):* The condition of the animals at the end of the 30-day period seemed quite as good as at the outset; there was no weight loss. Muscle showed no induration or slough; no deaths.

3. *Ergoklonin (concentrated 2×):* The birds showed minor weight loss but were not emaciated. Breast muscle became indurated after about 8 days but did not ulcerate; no deaths.

4. *Ergoklonin (concentrated 4×):* Considerable weight loss was observed in all but 1, although not to the degree seen in Group 1; the animals appeared ill after the first week; 2 deaths, probably from upper respiratory infection.

5. *Ergonovine (twice daily):* Nutrition remained good and animals appeared quite healthy. No induration or necrosis of muscle occurred; no deaths.

6. *Ergonovine (4 times daily):* Same as Group 5 except for 1 sudden death immediately after injection on the 30th day, cause of which was not determined by autopsy.

Condition of the Comb. 1. *Fluidextract of ergot:* One animal remained free of gangrene, but showed unrelieved blanching and moderate atrophy of comb. Gangrene of digitations 5, 6 and 7,

PLATE II.

A, Ergoklonin (normal concentration): Bluing reaction 1 hour after injection; cock had received 1.5 cc. intramuscularly twice daily during the previous 29 days (No. 164). *B*, Ergoklonin (normal concentration): Same animal 7 hours after injection which had produced the bluing reaction in *A*; there is complete restoration of the comb to a normal status (No. 164). *C*, Ergoklonin (concentrated 2×): Bluing and drooping of the comb 1 hour after injection on the 28th day of the experiment; cock had received 1.4 cc. of the concentrate intramuscularly twice daily during the previous 27 days (No. 140). *D*, Ergoklonin (concentrated 2×): Same animal 7 hours after injection which had produced the reaction shown in C; there is slight residual cyanosis and normal erectility is not restored (No. 140). *E*, Ergoklonin (concentrated 4×): Moderate atrophy and pallor after intramuscular injection of 1.8 cc. of the concentrate twice daily for 15 days (No. 112). *F*, Ergoklonin (concentrated 4×): Marked atrophy and pallor produced by intramuscular injection of 1.92 cc. of the concentrate twice daily for 29 days (No. 131).

involving the distal 2 to 4 mm., occurred in 2 but did not progress. There was advancement of the gangrene in all others, almost to the base of the digitations, accompanied by withering of the comb and wattles; in 2 animals, spontaneous amputation of digitations 6 and 7 occurred (Plate I, *C* and *D*).

2. *Ergoklonin (normal concentration):* Within 10 minutes after injection slight circumocular pallor appeared, followed by minor blanching of the root of the comb and wattles; in about 15 minutes the dorsal third of the comb was cyanotic and cold. Cyanosis spread ventralward over half or more of the comb during the next 15 minutes but in an hour had regressed considerably and at the time of the next injection the comb had resumed the original bright red color and warmness. No gangrene was observed in the group and combs maintained original size and erectility (Plate I, *A* and *B*).

3. *Ergoklonin (concentrated 2×):* The primary reaction to injection was similar to Group 2 but cyanosis of the dorsal third persisted to slight degree for 7 or 8 hours. There was considerable flaccidity of the comb in this group, most marked about 1 hour after injection and erectility was never quite regained before the next dose. Gangrene appeared in 4 birds, in 3 not progressing beyond the distal 2 or 3 mm. of digitations 6 and 7; 1 showed moderate advancement of the process 3 to 4 mm. farther, involving digitations 4 and 5 slightly (Plate II, *C* and *D*).

4. *Ergoklonin (concentrated 4×):* During the first week the reaction paralleled Group 3; thereafter a tendency toward continued pallor of the comb was noted with slight gangrene appearing in 4 of the animals which remained stationary, but there was moderate to marked atrophy of the comb, to lesser degree of the wattles (Plate II, *E* and *F*).

5. *Ergonovine (twice daily):* The primary reaction was similar to Group 2, more marked, however, and the cyanosis at the end of an hour was deeper, but there was complete regression within 7 hours. At the end of the 30-day period, the combs were entirely normal except for a tiny gangrenous patch, 1 mm. long, at the tip of digitation 7 in one bird This appeared on the 17th day and did not progress.

6. *Ergonovine (4 times daily):* No essential differences were noted between this and Group 5 except that no gangrene appeared; normal color and temperature were not quite restored between injections during the day but resumed normal state between the evening and the first morning doses (Plate I, *E* and *F*).

7. *Mechanical pressure:* Immediate deep cyanosis followed application of a heavy elastic band between the root of the comb and the cleft between digitations 4 and 5; this proceeded to early gangrene in 1 day, moderately advanced in 3. The necrotic portion of the comb was more moist than is the gangrene of ergotism, but was otherwise the same.

Histologic Appearances. Regarding the mechanism of gan-

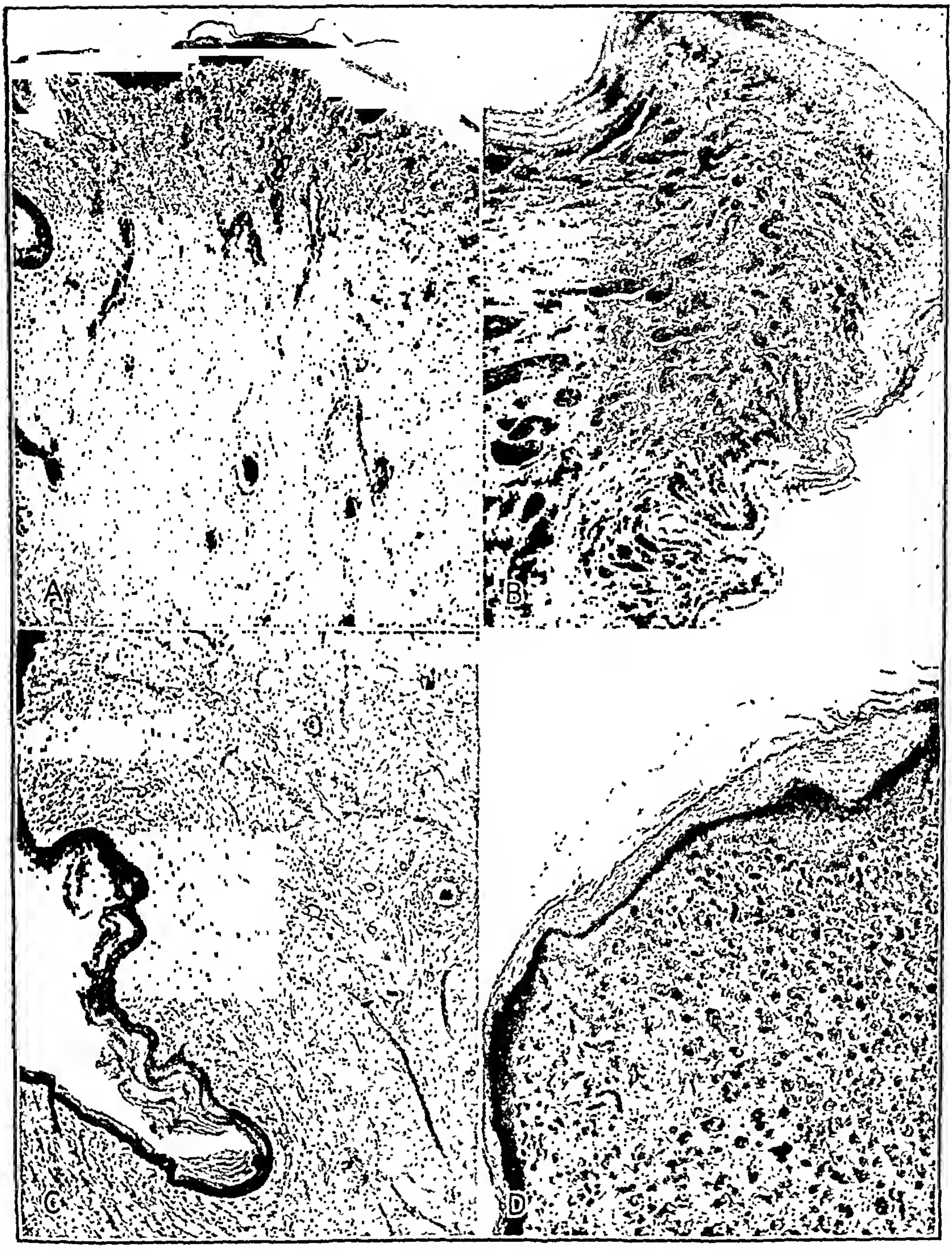


PLATE III.

(All photomicrographs magnified 69×.)

A, Normal control: Comb showing epidermis, cortical cavernous capillary bed and central loose connective tissue; note thick muscularis of central artery (No. 177). *B*, Mechanical gangrene of comb: There is necrosis of the epidermis; great dilatation of the capillary bed is accompanied by loss of endothelium and extensive thrombosis (No. 190). *C*, Ergonovine: Comb appears entirely normal, cock having been killed after resumption of normal color; animal had received 0.63 mg. of ergonovine intramuscularly twice daily during the previous 29 days (No. 167). *D*, Ergonovine: Comb of animal killed during the stage of cyanosis; capillary bed is dilated but endothelium is preserved and there is no thrombosis; epidermis is normal (No. 168).

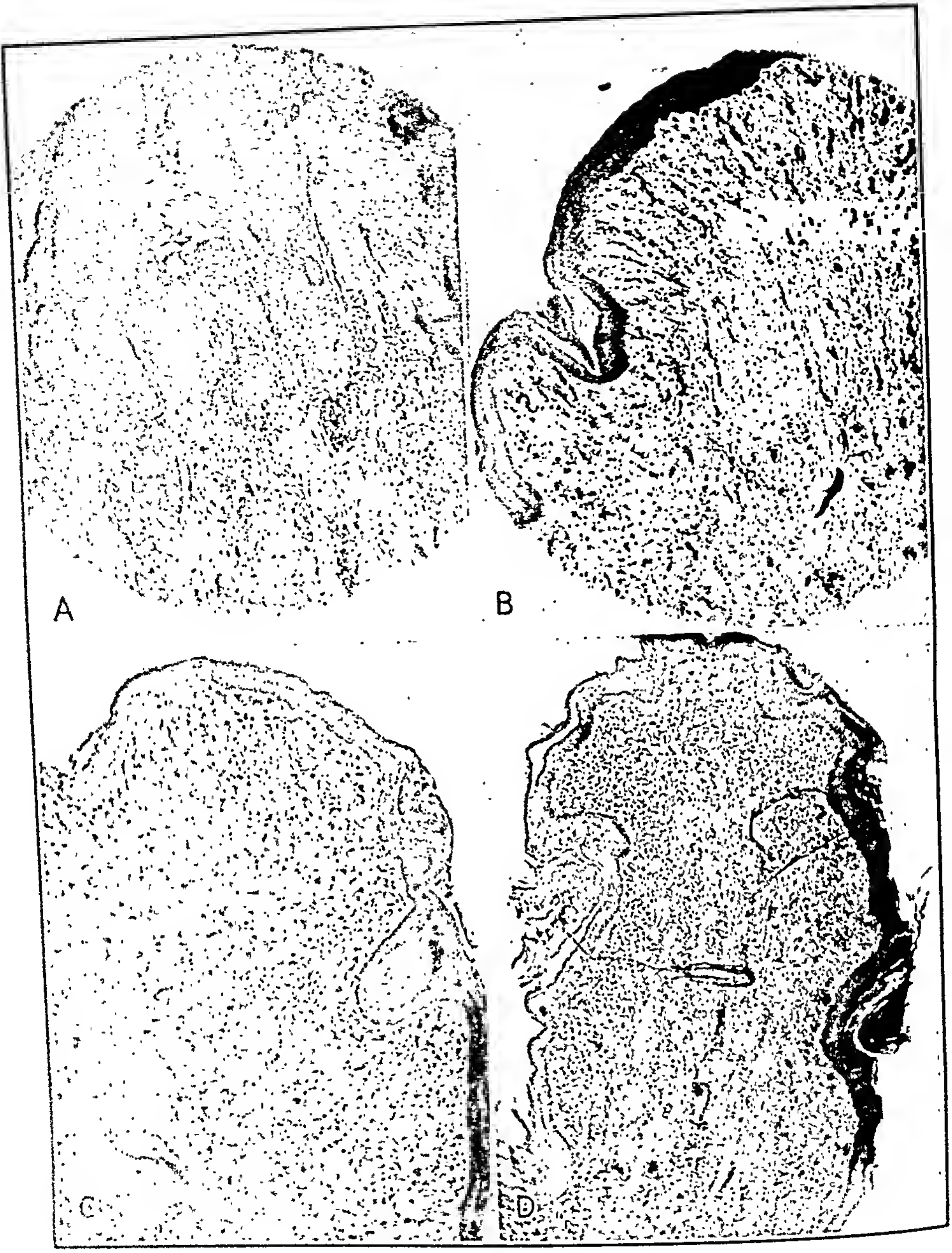


PLATE IV.

(All photomicrographs magnified 69×.)

A, Fluid extract of ergot: Comb at line of demarcation of gangrene showing dilatation and thrombosis of arteries and veins; cock had received 1 cc. twice daily for 17 days (No. 115). *B*, Ergokloun (normal concentration): Histologic appearances are normal after intramuscular injection of 1.42 cc. twice daily for 29 days (No. [illegible]). *C*, Ergokloun (concentrated 2×): Shows only minor dilatation of the capillaries but no necrosis after having received 1.06 cc. twice daily for 29 days (No. [illegible]). *D*, Ergokloun (concentrated 4×): There is atrophy and ischemia of the comb after receiving 1.52 cc. of the concentrate twice daily for 29 days (No. 131).

grene in the comb, the observations of Lewis are entirely substantiated. Primarily there is apparently an unrelieved arteriospasm with congestion, anoxemia and endothelial degeneration in the capillary beds, followed by stasis thrombosis therein and subsequent necrosis of the tissues. Propagation of thrombosis is followed by progress of the gangrene. Blood-vessels of the fowl present a considerably thicker medial muscularis than those of mammals, and cocks killed when the comb was cyanotic or blanched showed the arteries in a state of vigorous contraction, as evidenced by a relatively thicker wall in relation to the lumen, rugated elastica and more or less radial arrangement of intimal endothelium. It is perhaps for this reason that the cock's comb is unduly sensitive to the pharmacologic action of the ergot group. There was no evidence that the protracted administration of any of the drugs in this series produced permanent medial hypertrophy or arteriosclerosis. With the exception of the group receiving fluid extract of ergot, no visceral lesions analogous to changes in the comb appeared, save for ischemia in those animals killed during a period of generalized vasospasm. In the fluidextract group, 1 cock showed a small infarct of the myocardium and 3 presented liver degeneration with increase in interstitial tissue between the cords of liver cells; renal glomeruli were relatively ischemic as well. Essential changes in mechanically produced gangrene of the comb were the same as in ergotism.

Conclusions. While ergonovine and ergoklonin produce rapid and protracted contraction of the uterus, the coincident vasospasm (upon which the production of gangrene depends indirectly) is relatively fleeting. Vasospasm is comparatively unrelieved following administration of fluidextract of ergot, however, and gangrene of the cock's comb ensues. Even in the presence of moderately advanced gangrene of comb there is little or no visceral damage demonstrable.

One must realize that the dose of the drugs in these experiments is far in excess of that administered therapeutically. It is legitimate to state, then, that ergonovine and purified liquid preparations of ergot, standardized for their content of this alkaloid, may be used without fear of ergotism.

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ERGONOVINE VERSUS ERGOTAMINE AS A TERMINATOR OF MIGRAINE HEADACHES.*

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Confused thinking about migraine and disappointing results of treatment are due in part to a failure to define and to integrate the many factors involved. The ophthalmologist, the gynecologist or the psychoanalyst is apt to see the patient as a case of astigmatism, of dysmenorrhea or of mother fixation, and treating only that aspect, neither cures the patient nor does credit to his specialty.

Conditions Which Cause Seizures of Migraine.

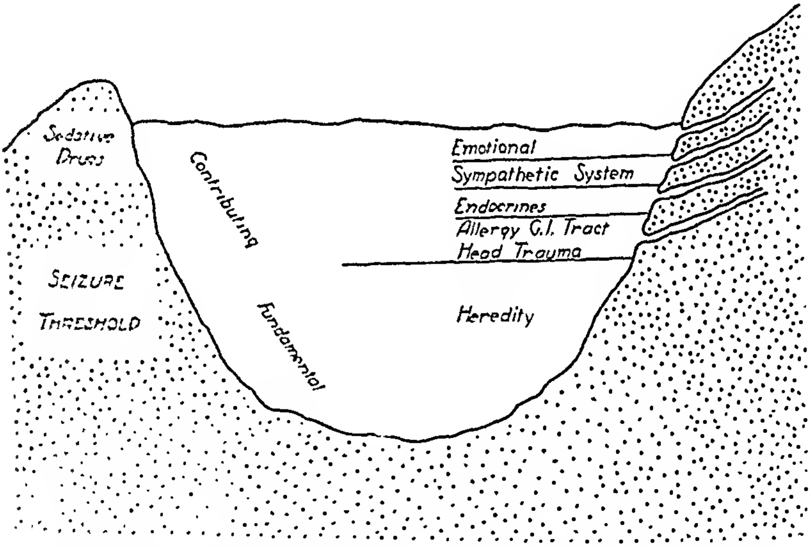

Fig. 1.—The various fundamental and contributory conditions which may cause seizures of migraine in the individual patient. A periodic increase of influences results in a periodic overflow of the reservoir; such overflow representing a migraine attack. Attempts at therapy should include the stopping of contributory factors and the elevation of the patient's threshold for pain.

Not only in any group of migraine patients, but also in each individual patient, multiple causes are, I believe, at work. In general, these are the same causes which produce epilepsy, but in different proportions. Many printed words can be saved by expressing the multiple factors in the form of a line picture. The conditions which combine to produce the symptom, migraine, may be represented as underground springs which feed a reservoir. When the waters of the reservoir rise, as they periodically do, and overflow the banks, this represents a migraine attack. Whether overflow occurs will depend in part on the number and size of the feeding springs, and in part on the height of the restraining banks. The problem of the physician is to discover and, if possible, to block the springs and also to elevate the patients' threshold for pain.

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* Aid was received from the Josiah Macy, Jr., Foundation.

The various causes of migraine, and their relative importance, not only differ from patient to patient, but also in the same individual from time to time. Later von Storch and I will attempt statistical analysis of the various causes encountered in our patients. For the present, without attempting to assign values, I show in the accompanying figure some of those factors which are considered of etiologic significance in migraine. This preliminary exposition is for the purpose of orientation and in order to place in its proper proportions what will be said about ergot.

Crude ergot in the treatment of migraine has had an occasional proponent. In 1898 Thomson[25] wrote "Ergot in full doses is superior to any other agent in arresting the headache," but whether because of ergot's histamine constituent or because of its instability, the drug has never held a recognized position on a shelf crowded with migraine remedies. In 1926 and later, several reports appeared in European journals favorable to the use of the alkaloid ergotamine tartrate. I began treatment of migraine with ergotamine tartrate 5 years ago, and since that time, my associates and I have administered the drug to 140 patients for the relief of an aggregate of thousands of headaches.[13,15] Injection of ergotamine tartrate terminates the headache of nine-tenths of our patients, a proportion also encountered by other authors, notably O'Sullivan[3,19] and Logan.[17]

Aside from the dramatic effect of ergotamine in the termination of headaches, the action seems to be specific for headaches of the migraine type.[16] Therefore the drug does more than increase the headache threshold—it temporarily blocks the inflow of waters which feeds the headache reservoir. On a subsequent occasion, however (perhaps even before the usual interval), the inflow resumes and the succeeding attack occurs. Ergot is not a "cure" for migraine. It is not even a means of preventing headaches, for injection of the frequent doses needed would be neither safe nor practical. Ergotamine affords speedy relief to the patient after the attack begins and an opening wedge to the investigator. Associates and I have reported certain laboratory studies of ergotamine tartrate.[21,22] The purpose of this paper is to record results obtained with another ergot alkaloid, ergonovine.

The isolation of a new and more active oxytocic alkaloid of ergot was announced during a short period of time from 4 different laboratories.[4,5,6,11,23,24] After some confusion over questions of priority and whether the substances were identical, the various workers agreed that they were.[12] The Council of Pharmacy and Chemistry adopted for the new substance the name of "Ergonovine;" the empirical formula is $C_{19}H_{23}N_3O_2$. Proprietary names have been selected by the various pharmaceutical houses.

Methods. The names, amounts and manufacturers* of the medicines which are mentioned in this paper are listed below. The dosage used had to be suited to the individual, but the maximum amount was ordinarily 1 ampule given intravenously and 2 tablets taken hourly until headache was relieved or 8 tablets had been taken. In the case of ergoklonin liquid, a teaspoonful was given hourly until relieved or 4 doses taken. The ampules are for injection and the tablets and liquid for oral administration.

Ergotamine tartrate (gynergen) (Sandoz) a 1 cc. ampule contains 0.5 mg. and a tablet contains 1 mg.

The various preparations of ergonovine are:

Ergobasine tartrate (Basergin) (Sandoz), a 1 cc. ampule contains 0.2 mg. and a tablet contains 0.25 mg.

Neo-gynergen (Sandoz), a 1 cc. ampule contains 0.25 mg. ergotamine tartrate and 0.125 mg. ergonovine (ergobasine tartrate) and a tablet contains the same.

Ergoklonin (Wyeth), a 2 cc. ampule contains 0.4 mg. ergonovine and liquid for oral use contains 0.4 mg. per 4 cc.

Ergometrine (Burroughs-Wellcome), a 1 cc. ampule contains 0.5 mg. and tablet 0.5 mg.

Ergotrate (Eli Lilly), a 1 cc. ampule contains 0.2 mg. hydracrylate of ergonovine.

Patients were those attending the migraine clinic at this hospital or were private patients. Most of these had already received treatment with ergotamine tartrate, results of which in 120 patients have been published.[15]

Results. Observations of the clinical effect on patients extend over the past 2 years. Tabulation based on the total number of headaches treated would be unfairly weighed with successful results, since only those who were helped continued to take treatment. The first trial is usually prophetic of the usefulness of an ergot preparation. The therapeutic results include not only the effect on the existing headache, but also the patient's attitude towards the magic disappearance of his pain. Instead of being jubilant, some patients seem unimpressed and complain of some unpleasant symptom, which precludes continued use of the drug. Seemingly, subconsciously, they cling to their headaches. Ordinarily, only the results obtained from the initial administration of the drug were counted, but in those cases in which different preparations of ergonovine were used, or in which the severity of headaches varied markedly, an average result of the different trials was set down.

Seventy-eight different patients received treatment for migraine headache with one or more of the various preparations of ergonovine. The results are presented in Table 1, together with comparable data for 140 patients who received treatment with ergotamine.

Parenteral Administration. Fifty-four patients received injection of one of the ergonovine preparations during headache, 39% of these administrations resulted in complete cessation of the headache and other symptoms. In 40%, the headache was only partially relieved or was stopped, but later returned. In 17% headache was not affected, and in 4% it became worse. Patients who were relieved found the time interval between injection and the beginning of relief about the same as for ergotamine tartrate, namely 30 to 60 minutes. This is in contrast with the fact that ergonovine affects uterine contractions much more promptly than does ergotamine tartrate.

These results may be contrasted with those for ergotamine. In 140 cases in which von Storch or I have administered ergotamine parenterally, the headache was stopped completely in 89%, improved in 5% and not improved or became worse in 6%. Therefore ergonovine was less than half as effective as ergotamine in terminating headaches, though if complete failures are compared, ergonovine's showing was not so unfavorable, 21% of failures, against ergotamine's 6%.

Oral Administration. Information concerning the drugs taken by mouth is not so reliable, because the immediate effect was not witnessed by the author. The results (Table 1) probably err on the favorable side, because some patients who were not benefited by the injection of ergonovine did not take it by mouth, and because those who did, but were not benefited, were less likely to return for renewed supplies and to report results. Table 1 is more useful for the comparison of different drugs than for the comparison of routes of administration. The two ergot alkaloids yielded practically the same results when taken by mouth, a similarity not observed when the drugs were injected. The fact that ergotamine is absorbed with difficulty from the gastro-intestinal tract, and ergonovine is readily absorbed, probably accounts for the differences observed.

TABLE 1.—EFFECT OF THE ADMINISTRATION OF ERGONOVINE AND OF ERGOTAMINE ON MIGRAINE HEADACHE.

Route.	Drug.	No. of patients.	Percentage.			
			Well.	Improved.	Not improved.	Worse.
Parenteral . .	Ergonovine	54	39	40	17	4
	Ergotamine	140	89	5	4	2
Oral	Ergonovine	42	43	24	33	0
	Ergotamine	56	41	27	30	2

These results indicate that injection of ergonovine is less than half as effective as ergotamine tartrate in completely aborting migraine headaches. However, of migraine patients who are relieved by ergonovine, many prefer ergonovine to ergotamine, either, because they experience fewer gastric symptoms, or because relief may be had from the ingestion of the drug.

Occasionally, a patient whose headache is ordinarily relieved by injection of ergotamine will have an unusually severe headache which ergotamine does not terminate. In such a desperate situation, I have repeatedly found that the intravenous injection of 2 cc. of the amidopyrine compound "cibalgine" would complete the relief.

Gastric Symptoms. Aside from welcome release from headache by means of ergot, an important question concerns the unpleasant symptoms which a patient may experience. Sensations of muscle soreness and of fatigue are certainly more common after ergotamine than after ergonovine. The most frequent symptoms are nausea and vomiting. Adair[1] and colleagues encountered vomiting "but rarely" in postpartum patients given 0.2 mg. ergonovine. My results with ergonovine and with ergotamine (including data for ergotamine reported by Lennox, von Storch and Solomon[16]) are shown in Table 2. Migraine patients who had nausea and vomiting before the drug was given are not listed as positive, unless an increase of symptoms resulted.

TABLE 2.—PROPORTION OF PATIENTS HAVING NAUSEA OR VOMITING AFTER ADMINISTRATION OF ERGOTAMINE OR ERGONOVINE.

Patient's headache.	Ergotamine tartrate I.V.			Ergonovine I.V. and P.O.		
	No. of cases.	Percentage having:		No. of cases.	Percentage having:	
		Nausea.	Vomiting.		Nausea.	Vomiting.
Without headache	38	47	18	21	24	4
Non-migraine	46	56	37	18	50	11
Migraine	110	78	57	64	58	25
All cases	104	67	45	103	50	18

Inspection of the table shows that patients having migraine headaches, vomited less than half as frequently after ergonovine, as after ergotamine. Since ergonovine is less than half as effective as ergotamine in terminating migraine headaches, the question arises whether ergotamine acts by inducing vomiting.

However, separate tabulation of those cases receiving ergonovine in which the effect, both on headache and on the gastric symptoms was clear cut, showed that patients who obtained complete relief from the use of ergonovine, had even less nausea and vomiting than those not relieved.

No. of cases recorded.	Percentage experiencing:	
	Nausea.	Vomiting.
31	45	31
21	57	43

constriction of peripheral vessels leading to occlusion. Such fears have been augmented by reports of gangrene, after the administration of ergotamine to patients with serious liver damage or with septic infection.[9,20,26] In the treatment of migraine patients, such fears have been without substantial grounds, either in our experience or that of others. Practically every one of the migraine patients coming under the care of my associates and myself in the past 5 years, including cases with essential hypertension and arteriosclerosis, have received ergotamine. Some have taken it for nearly 5 years, some require several ampules weekly, 2 elderly women with status migraine have each taken hundreds of injections; but we have never encountered more than transient symptoms of an inadequate peripheral circulation. Most writers agree that the injection of ergotamine tartrate causes a moderate, temporary increase in systolic and diastolic blood pressure. We have seen or heard of no cases in which ergotamine seemed to be the cause of a continued high level of blood pressure. However, judgment on the ultimate effects of ergot on the vascular system must await the accumulation of evidence over a period of many years.

Because the tonic action of ergonovine on the smooth muscle of the uterus is so prompt and prolonged, the effect of ergonovine on blood pressure requires careful examination. Adair and his associates[1] measured blood pressure in a "considerable number" of parturient women. Their data indicate an average rise of 5 mm. systolic and a fall of 3 mm. diastolic pressure. The time interval after injection was not given. On the other hand, Cushny[7] states that ergonovine causes increase of blood pressure.

My associates, Dr. Page Newbill, Hildegard Leonhardt, Doris Thaler, and I measured the blood pressure before and at short intervals for an hour after the intravenous administration of ergonovine in migrainous and other patients. These data, and similar information concerning ergotamine, are gathered in Table 3. The table records the average figures for the various groups; the blood

TABLE 3.—AVERAGE MAXIMUM INCREASE OF BLOOD PRESSURE AND DECREASE OF PULSE RATE FOLLOWING ADMINISTRATION OF VARIOUS DRUGS WHICH INFLUENCE MIGRAINE.

Drug.	No. of cases.	Systolic B.P.		Diastolic B.P.		Pulse rate.	
		Initial.	Increase.	Initial.	Increase.	Initial.	Decrease.
Ergotamine I.V.	62	120	19	76	16	85	16
Ergonovine I.V.	35	117	14	77	10	76	4
Ergonovine P.O.*	23	118	6	78	7	74	6
Epinephrine S.C.	14	126	25	84	7†	81	27‡

* Twelve cubic centimeters ergonovine (ergoklonin) given per os.
† Decrease.
‡ Increase.

pressure and pulse rate before the drug was administered, and afterwards the highest readings of the systolic and of the diastolic blood pressure, and the lowest pulse rate. The maximum systolic reading did not always coincide with the maximum diastolic.

Regarding blood pressures, ergotamine tartrate, when injected intravenously in 62 patients, resulted in an average maximum rise of 19 mm. systolic and of 16 mm. diastolic. This diastolic rise is the same as obtained by Freeman and Carmichael[8] in a group of 24 normal subjects, whereas our systolic rise is 6 mm. greater. Following intravenous injection of ergonovine, the average maximum increase of systolic pressure was 14 mm. and of diastolic pressure 10 mm., a smaller increase than occurred after ergotamine. Ergonovine (ergoklonin) taken by mouth caused relatively slight alterations, an increase of 6 mm. systolic and 7 mm. diastolic. The blood pressure changes experienced by 14 patients following subcutaneous injection of 0.1 mg. epinephrine are included for comparison. Ergotamine and ergonovine caused no significant change of pulse pressure, whereas the increase after epinephrine was great.

The distribution of the changes in systolic blood pressure readings is also of interest. An insignificant increase in systolic pressure (less than 11 mm.) occurred in 48% of patients after ergonovine and in 37% after ergotamine. An increase in systolic pressure between 11 and 20 mm. was noted in 40% of patients after ergonovine and in 29% after ergotamine. Increases of pressure exceeding 20 mm. occurred in 12% of patients after ergonovine and in 34% after ergotamine. The changes in blood pressure may vary greatly from time to time. For example, Mrs. W. had the following maximum increases in systolic and diastolic pressures, respectively: after neogynergen 6 and 26; after ergonovine on three occasions 22 and 26; 65 and 65; 3 and 0.

Is the increase in systolic blood pressure dependent on the initial pressure? Tabulation of this point for patients receiving intravenous injections of ergotamine and ergonovine showed that subjects with an initial pressure above 130 had a relatively small increase of pressure. Two patients, who received ergotamine intravenously, had initial systolic pressures of 195 and 230 mm. respectively. The maximum readings after the injection were respectively, 7 and 4 mm. lower. Meakins[9] and associates have used ergotamine in the treatment of hypertension.

Is the increase in blood pressure a prerequisite for relief of headache? Tabulation indicated the lack of any positive correlation. The increase in systolic pressure was 13 mm. for patients who were relieved, 17 mm. for those not relieved and 19 mm. for those without headache when the test was made.

Pulse Rate. Changes in pulse rate seem of little interest to the clinician, but are of moment in attempted explanations of the mechanism of migraine attacks and of their relief by the ergot alkaloids. The decrease in pulse rate after administration of ergotamine is well recognized, and has been generally attributed to a paralyzing effect on those sympathetic nerves which increase the rate of the heart. Youmans and associates,[28] however, believe bradycardia is due to vagus stimulation, as the effect in human subjects is abolished by atropine.

The data in Table 3 indicate that the intravenous injection of ergotamine was followed by a pronounced fall in pulse rate (in 62 patients an average maximum fall of 16 beats). The average maximum fall after the injection of ergonovine was only 4 beats and after its ingestion 6 beats. After epinephrine injections, the average maximum increase was 25 beats.

Tabulation of the distribution of changes showed a decrease of less than 10 beats in 76% of cases receiving ergonovine injections against 27% receiving ergotamine. There was a bradycardia of more than 20 beats in no case receiving ergonovine and in 30% of cases receiving ergotamine.

Youmans and associates[27] believe the effect of ergotamine is more pronounced when the sympathetic nervous system had been stimulated by epinephrine. Is the degree of bradycardia in our observations dependent on the initial pulse rate? And, if so, can the more marked bradycardia in the group receiving ergotamine be due to a larger number of patients with a high initial pulse rate? Tabulation bearing on this point follows.

	Ergotamine.		Ergonovine.	
Initial pulse rate.	No. of cases.	Average decrease of pulse rate.	No. of cases.	Average decrease of pulse rate.
Less than 80	23	9	25	2
80 to 99	21	19	13	9
100 and over	12	29	0	0

True, bradycardia is greater, at least in absolute numbers, when the initial pulse rate is high. Also it happened that only patients who were to receive ergotamine had an initial pulse rate above 100. However, these circumstances but partially explain the differences in the average maximum decrease for the two groups. Even those patients whose initial pulse rate was below 100, had less bradycardia after injection of ergonovine, than after injection of ergotamine.

Can improvement in headache be correlated with the presence of bradycardia? There is some such correlation, both in point of time after injection and statistically. Subjects without headache had a decrease of 13 beats. Those who obtained complete relief from their headache had a greater fall of pulse rate (12 beats) than patients not relieved (7 beats). However, the smaller decrease in unrelieved patients was due, in part, to the fact that these had an average initial pulse rate 6 beats slower than patients who were relieved.

Other Circulatory Symptoms. In addition to changes in blood pressure and pulse rate, occasionally patients complained of symptoms which have to do with circulation. Transitory tingling of the fingers and congested appearance of the hands have been encountered after ergonovine, as well as after ergotamine injections, though not, I think, so frequently. The same is true of precordial pains. Complaints of precordial pains coincided in time with the maximum changes in blood pressure, but were not confined to those occasions in which pronounced increases in pressure occurred.

One very unusual patient was Mrs. T., who had a history of chronic headache of a questionable migraine type, and who was subject to attacks of the following symptoms: severe pain in the left groin, left hemiparesis and parasthesia of central origin, followed by an elevated blood pressure, by precordial pain and cardiac asthma. In one of these attacks the region of the left femoral artery had been explored with the expectation of finding an embolus but instead the artery was constricted. We believed she had paroxysmal contraction of the arteries of the brain and leg. I gave her ergonovine intravenously as a diagnostic test of her headache. Three minutes after the injection she complained of paræsthesia of the left side of the body and face. Six minutes later she had precordial pain and the blood pressure was increased by 17 mm. systolic and 20 mm. diastolic. After an hour, the symptoms continuing, the patient had one of her attacks of cardiac asthma which was relieved by inhalation of 10% of carbon dioxide and 90% oxygen, a mixture which is most effective in dilating arterioles of the brain. During the attack the affected left limb felt colder than the right and pulsations of its arteries could not be felt. I was unable to secure blood from the internal jugular vein. In this patient subject to attacks of arterial spasm, an attack was precipitated by an injection of ergonovine.

Comment. Ergotamine and ergonovine in their therapeutic action on migraine headaches and also in their effect on blood pressure and heart rate act in the same direction. Differences between them in the respects mentioned are quantitative and not qualitative. In another communication Leonhardt and I[14] have shown that ergotamine and ergonovine, both cause increase in the flow of blood through the arm and an increased concentration of both arterial and venous blood. The changes in blood concentration (like the relief of pain, and the changes in blood pressure and in heart rate) were less pronounced following the administration of ergonovine. The termination of headaches by ergot alkaloids cannot be explained directly by anyone of these circulatory changes, for similar or greater changes in blood pressure, in blood flow, in blood concentration and in heart rate can be brought about by other agencies which do not stop migraine headaches. Nevertheless, these various alterations acting together and in combination with other, as yet unstudied, influences may eventually be explanatory of the mechanism of migraine and of its relief.

These present observations indicate that the ergot alkaloids do not help headache by virtue of a paralyzing action on the sympathetic nervous system, thereby either permitting the dilatation of spastic cerebral vessels or the anesthetizing of pain-carrying sensory nerve fibers. Rather ergotamine and ergonovine seem to be stimulating, causing a "tightening up" of the blood vascular system. Of particular value are the observations of Graham and Wolff[10] of a decreased amplitude of the pulsations of the temporal arteries at the time migraine patients were relieved of headaches by means of ergotamine.

The evidence that I have presented indicates that the oxytocic principle in ergot is not the principle which helps migraine headaches. Rather, the helpfulness of ergot seems to reside in the fraction which effects the contraction of arteries and the depression of the heart rate.

Ergonovine seems to have a distinct advantage over ergotamine in the treatment of puerperal states where a maximal effect on the uterus and a minimal effect on the arteries is desired. Probably, the specific and dramatic influence of ergot on migraine headaches cannot be secured without that fraction of ergot which influences the tone of arteries. Because migraine is a chronic condition persisting in many patients throughout life, and because those whose lives have been made livable by ergotamine are loathe to give it up on the mere suspicion of possible harm lurking in the dim future, there is need of intensive study of the effect of ergot alkaloids on the morphology and the physiology of arteries. In the Middle Ages epidemics of St. Anthony's fire from the consumption of grain spoiled by ergot had a convulsive and a gangrenous form.[2] Was the appearance of gangrenous ergotism in any way influenced by predisposition from race or from circumstances? What migraine patients, if any, should be refused the help of ergot alkaloids? What are the criteria for stopping ergot therapy once it is started? We, as yet, do not know the answer to these questions.

Each patient with migraine must be treated as an individual. There are tractable and intractable headaches. There is a powerful migraine pain killer (ergotamine) and one which is relatively weak (ergonovine). An elephant gun should not be trained on a rabbit and, if ergonovine proves effective, there is no need to prescribe ergotamine. Patients who find ergonovine effective usually prefer it, either because gastro-intestinal symptoms are not so pronounced or because relief follows oral administration. Ergotamine does not seem to have strong action as an abortifacient. Several migraine patients have continued to use it in pregnancy without ill effect. Ergonovine, on the other hand, should not be used during pregnancy.

In a disorder so stubborn as migraine and in dealing with patients who are so hard to hold, the more weapons the physician has the better. Though far from being as effective as ergotamine, ergonovine can be useful in special situations. Ergotamine, ergonovine and non-habit forming sedative drugs should be prescribed in accordance with the needs of the individual. No drug, no matter how gratefully received, should be allowed to dull the physician's interest in finding, and if possible, removing the causes of the migraine.

Conclusions. Ergonovine has been used in 78 patients suffering from an attack of migraine headache. The injection of ergonovine terminated headache in 37% against 89% of patients receiving injection of ergotamine tartrate. Ergonovine brought partial or temporary relief to an additional 40% of the patients. The proportion not helped at all was 21% after ergonovine and 6% after ergotamine.

Ergonovine taken by mouth, while less effective than when injected, is relatively more effective than ergotamine tartrate taken by mouth.

Ergonovine causes slight increase of systolic and of diastolic blood pressure and a slight decrease in pulse rate, the average change being only about half the alteration observed following administration of ergotamine tartrate. The specific usefulness of ergotamine and ergonovine in the successful termination of migraine headaches is not related to their oxytocic action, but probably bears a relationship to the action of the alkaloids on the blood vascular system.

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DIAZOMETHANE POISONING.

FIRST CLINICAL CASE REPORT.

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So far as we are aware this constitutes the first clinical report of poisoning from diazomethane. References to the extreme toxicity of the gas and the symptoms produced by it have been confined almost exclusively to brief statements in the chemical literature. In view of the increasing use of diazomethane it would seem desirable to direct attention to the hazards of exposure to this reagent and to report one case of poisoning from it which has come under our observation.

Under ordinary conditions diazomethane is a gas, easily soluble in benzene or ether. Dissolved in these solvents it has proved to be a valuable reagent in the synthesis of organic compounds since it yields products of methylation quantitatively at room temperatures and without the assistance of other reagents. Owing to the expense in preparation, diazomethane has apparently not found many commercial applications. However, as a laboratory reagent the use of this compound has increased during the past few years to such an extent that methods for its preparation have been included in recent elementary manuals of organic chemistry.

Case Report. The patient is a male, aged 27, and a graduate student in organic chemistry. In the course of his laboratory work he elected to prepare trimethylbarbituric acid by allowing diazomethane to react with barbituric acid. The diazomethane was prepared by adding a concentrated solution of potassium hydroxide to nitrosomethyl urea and collecting the gas, CH_2N_2, in ether according to the procedure described by Arndt.† The ether solution containing the diazomethane was added directly with gentle stirring to barbituric acid at room temperature and 1, 3, 5-trimethylbarbituric acid was precipitated and nitrogen evolved.‡ Since diazomethane

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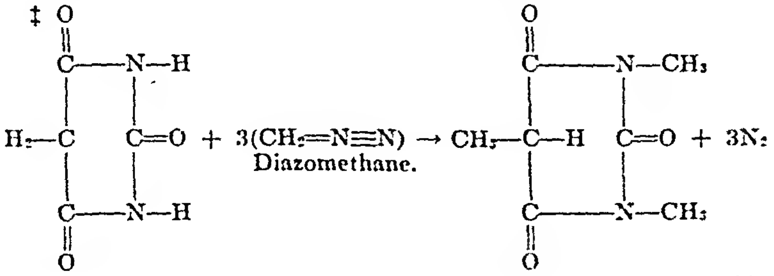
* Porter and Scott Fellow in Medicine.

† $CH_3N(NO)CONH_2 + KOH \rightarrow CH_2N_2 + KCNO + 2H_2O$.
Methyl nitroso urea. Diazomethane.

‡ 

Barbituric acid. 1. 3. 5 Trimethylbarbituric acid.

is very volatile, the evolved nitrogen undoubtedly entrained some diazomethane.

Our patient neglected to conduct any of these procedures under a hood. While he may have inhaled some of the diazomethane while preparing the ether solution, nevertheless, it was while he was stirring the reagent into the barbituric acid that he suddenly became choked, dyspneic, and developed a violent, non-productive cough. The patient went to his home, where this attack continued for 3½ hours and gradually subsided. For the next 2 days he had paroxysms of dyspnea and coughing which recurred without any apparent reason. On the third day after exposure he developed a particularly violent paroxysm of coughing and orthopnea. Administration of ephedrine by his family physician afforded little relief.

During this time the patient was unable to retain food. Ingestion of food produced distention which he claimed interfered with his breathing and caused him to vomit. He also developed soreness of the abdominal muscles which he attributed to the labored breathing and retching.

On the sixth day after exposure to diazomethane the patient was admitted to this hospital in very grave condition. He had, according to report, neither slept nor eaten for 4 days. He was cyanotic, orthopneic, cold and dripping with sweat. The pulse was feeble and the rate was 132 per minute. The patient's chest lacked somewhat in resonance, and scattered throughout it were numerous musical and bubbling râles suggestive of pulmonary edema. Heart sounds were hardly audible. Following repeated injections of adrenalin and opiates the patient's condition improved greatly during the following day.

At this time the cough became productive of a thin, watery sputum which contained eosinophils, squamous epithelium, alveolar cells, Charcot-Leyden crystals and numerous bacteria. The blood count on admission was as follows: erythrocytes, 4.5 millions per c.mm.; hemoglobin, 14.2 gm. per 100 ml.; leukocytes, 10,800 per c.mm.; and a differential count of 76% neutrophil cells, 10% lymphocytes, 10% monocytes and 4% eosinophils. A week later the leukocyte count was decreased to 5800 and the differential count was essentially the same with 5% eosinophils present. The urinalyses on admission revealed a moderate albuminuria which became decreased to a barely perceptible amount without the following week. On spectroscopic examination of the blood only the bands of oxyhemoglobin were observed. Analyses of the blood and blood serum for urea nitrogen, sugar, chloride, CO_2, uric acid, cholesterol and bilirubin yielded concentrations within the normal range of values for these respective components.

On the day after admission a roentgenogram of the chest showed unusual prominence of the trunk shadows. A film made a week later revealed an unusual degree of hyperventilation of the lungs and a corresponding increase in the prominence of the trunk shadows.

An electrocardiographic tracing revealed a slurring of the *QRS* complex and a low *T* wave in Lead I. The pulse rate after the first 3 days following admission was between 90 and 100 per minute and the temperature which had been slightly elevated fell to a normal level.

The possibility was considered that poisoning with diazomethane might be related to the liberation of methyl alcohol. No disturbances in vision, however, were noted and the eyegrounds remained normal throughout the period of hospitalization.

The patient's condition in the hospital gradually improved so that within 2 weeks after the accident he became entirely free from attacks of dyspnea and coughing and after another week was discharged from the hospital. Repeated physical examinations of the heart and lungs during the week before discharge yielded essentially normal findings. The patient has removed to a distant locality and no recent follow-up examination has been obtained. However, 4 months after his exposure to diazomethane he reported that there had been no recurrence of symptoms.

Comment. Diazomethane was discovered in 1894 by Pechmann[10a] who described it as being extremely poisonous, causing air hunger and chest pains. In a later article[10b] in 1895 he stated that he had been delayed in making further experiments on the compound owing to the poisonous effect that the gas had produced on him.

Corroborating Pechmann's observations, Bamberger and Renauld[3] in 1895 reported that they also had experienced toxic effects in experimenting with the gas and that their symptoms were essentially dizziness and tinnitus aurium.

In addition to these symptoms, Gottstein, Schlossmann and Teleky[6] reported that diazomethane produced denudation of the skin and mucous membranes. These authors claimed that the action of diazomethane was similar to that of dimethyl sulphate. Loring[8] also reported that the vapors from the ether solution of the gas were very irritating to the skin and rendered the fingers so tender that it was difficult to pick up a pin.

Arndt and Amende[2] in 1930 reported that 2 individuals were affected by the slightest traces of the gas, developing chest pains, fever and severe asthmatic symptoms about 5 hours after exposure to the gas. Arndt[1] described diazomethane as being "an especially insidious poison." He stated that "a person may work with it carelessly for some time without noticing effects. This leads, however, to a supersensitivity so that it is almost impossible to work even carefully with diazomethane without being subjected to attacks of asthma and fever."

The toxicity of diazomethane has been attributed by Flury and Zernik[5] to the intracellular formation of formaldehyde. Diazomethane reacts slowly with water to form methyl alcohol and liberate nitrogen.* Formaldehyde, in turn, is formed by the oxidation of methyl alcohol. The possibilities of liberation *in vivo* of methyl alcohol or of the reaction of diazomethane with carboxylic compounds to form toxic methyl esters may be considered;† on the other hand, the deleterious effects of diazomethane may be primarily due to the strongly irritant action of the gas on the respiratory system.

In addition to the toxicity of diazomethane, the explosive nature of this compound represents another hazard. Staudinger and Kupfer[11] reported that either in the gaseous or liquid state diazomethane exploded with flashes. Even at −80° C. Steacie[12] found that liquid diazomethane detonated. Several other investigators[4,7,9] have also directed attention to the explosive nature of this compound. It has been the general experience, however, that explosions

* $CH_2N_2 + H_2O \rightarrow CH_3OH + N_2$.

† $RCOOH + CH_2N_2 \rightarrow RCOOCH_3 + N_2$

do not occur when diazomethane is prepared and contained in solvents such as ether or benzene.

Animal Exposure to Diazomethane. Very little has been published on the toxicity of diazomethane for animals. Flury and Zernik[5] reported that an exposure of cats for 10 minutes to the gas in a concentration of 0.3 mg. per liter (about 175 parts per million) was followed within 3 days by death. The lungs of the cats showed hemorrhage, emphysema and edema.

To study its effect on animals, we attempted to secure a known low concentration of diazomethane mixed with air alone and free from volatile organic solvents. In accordance with the observations of others, however, we found mixtures of diazomethane with air alone to be violently explosive. The diazomethane in the experiments reported by Flury and Zernik was dispersed from a 2% solution of the gas in ether. Our experiments would indicate that this is probably a safer method of testing the toxicity of the gas.

In one of our experiments 2 cc. of 50% potassium hydroxide solution was poured over approximately 0.2 gm. of nitrosomethyl urea in the bottom of a 5-liter desiccator with an outlet open to the air. A guinea pig had previously been placed on a platform in the desiccator. After the introduction of the alkali, the guinea pig immediately began to strike its nose with its forepaws and to experience difficulty in breathing. Typically labored, asthmatic type of respiration ensued. After 25 minutes in the desiccator the pig was returned to its cage where it was found dead an hour later. Autopsy revealed inflated lungs from which on section edematous fluid oozed out. Histologic sections of the lungs showed a marked precipitable edema in the alveoli and bronchioles without appreciable congestion or swelling of the alveolar epithelium.

The pulmonary symptoms observed in diazomethane poisoning may be explained either on the basis of a true allergic sensitivity after repeated exposure to the gas, and particularly in individuals of allergic heredity; or on the basis of a powerful irritant action of the gas on the mucous membranes of the lungs. To support the former possibility is the statement by Arndt that individuals who had first handled the gas with relative impunity later experienced symptoms on even the slightest exposure. In the patient here reported a clear-cut history of asthma was obtained from his father and the patient himself reported that at times he had suffered mildly from hay fever. The only explanation, however, for the pulmonary lesions that we observed in the guinea pig after a primary exposure to the gas would appear to be that of a direct irritant action.

Summary. A case of poisoning by diazomethane is reported and attention is directed to the dangers of exposure to this gas.

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ACQUIRED SENSITIVITY TO CINCHOPHEN.

A REPORT OF SIX CASES AND A REVIEW.

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CLINICIANS know that thousands of people are able to take cinchophen (phenylcinchonic acid) and its compounds under a variety of conditions and over long periods of time, without apparent illness or injury. White[29] has estimated the consumption within the United States to be about 90,000 pounds yearly. Considering this widespread use, minor disturbances have occurred in only a small percentage of persons who use it, and only a fraction of 1% ever come to a fatal end as far as actually reported cases are concerned.

However, despite all the testimony as to the apparent harmlessness of cinchophen, the frequency of reports of toxic cirrhosis definitely attributed to its use are increasing rapidly. Many unreported cases have been discussed with physicians throughout this country, and several pharmacists have reported skin rashes after the use of this drug. The reason why more cases have not been reported will be explained later.

In this review, an effort will be made to demonstrate some striking examples of an acquired sensitivity, or susceptibility, to cinchophen and its compounds. Case reports will be presented which illustrate in a dramatic way reactions which followed immediately upon readministration of this drug or its derivatives. No evidence of toxicity, however, had occurred upon the first administration, even of large doses and over long periods of time. The apparent manifestations of cinchophen poisoning fall, in general, into several well-defined groups. In this report, and the 6 new cases, two groups are studied: (1) Cutaneous group of 10 cases with 2 deaths; (2) hepatic group of 22 cases with 12 deaths.

The mechanism by which one acquires a sensitivity from nonprotein substances such as cinchophen is not understood. This problem has been investigated by Landsteiner,[9] who was able to combine many of these substances with homologous animal sera and thus create compound proteins which have an immunologic activity comparable to a foreign serum. Antibodies have not been demonstrated, but Landsteiner[10] and others believe that an antigen antibody mechanism explains drug hypersensitivity, though it has not been proven.

Acquired sensitivity, or the appearance of toxic symptoms when cinchophen compounds were given in courses or intermittently, has been observed and reported by Weir and Comfort,[27] Bloch and Rosenberg,[2] Quick,[18] Davis,[3] Short and Bauer,[24] Palmer and Woodall,[14] Fink,[5] and others. Many cases appeared to show idiopathic or non-acquired sensitiveness, but the previous use of the drug could not be ruled out because of the large number of compounds on the market under different names, all containing cinchophen in varying percentages.

According to Hench,[7] it is a constituent of over 500 remedies advertised in American literature as cures for rheumatism, or as uric acid solvents. The best known of these preparations are atoquin and tolysin. Previous exposure, therefore, could have taken place without the knowledge of the patient; he might thus have become sensitized shortly after the first administration of the substance.

We have been impressed by this phenomenon, that although an individual does not show apparent toxic symptoms from cinchophen, damage may have occurred which may be accentuated by the second or third dose later on, even after several months or years. Willcox[30] first directed attention to the time factor which varies in length between the use of the drug and the first appearance of symptoms. The latter have frequently appeared weeks or months after the discontinuance of cinchophen, thus resembling the delayed effect seen in chloroform poisoning. It is also a common observation that a drug may be well tolerated for many weeks or longer, and then for some unknown reason the individual becomes receptive to its sensitizing action, and evidences of toxicity occur. Some allergists term this the refractory or delayed period of sensitization. This period may last for years for some, and days or weeks for others. This might explain why certain patients were noted who took cinchophen in a wide range of dosage at one time without symptoms, and later took the same amount or even a smaller dose, and became toxic. This theory in the future may lead to some interesting discoveries.

Lambert[illegible] remarked some years ago that one reason that acute yellow atrophy of the liver was much less often diagnosed, was that in the beginning it was not of the stormy type which physician had been taught to expect. Apparently the universal teaching in medical schools had been to diagnose all degrees of jaundice most often as the catarrhal type.

This observation may help to clarify the obscurities of cinchophen poisoning and explain the infrequency of its diagnosis throughout the country. The relationship between cinchophen and toxic cirrhosis has not been understood until recent years, even in the presence of jaundice, and toxic cirrhosis without jaundice has not been appreciated at all. Most of the cases so far reported have come from large medical centers and it is unreasonable to suppose that they did not occur elsewhere.

The present review of acquired sensitivity to cinchophen was made after an inquiry into the records of most of the large hospitals in New York. A study was made of the deaths from liver disease in which autopsy reports were obtained, and of other fatal cases with obvious liver disease on which autopsies were not performed. This study did not yield much information as to the relationship between drugs and death from failure of liver function for several reasons: 1, Because of the lack of an accurate history of the patient's use of any drug; and 2, because of the lack of knowledge on the part of the attending physician that cinchophen compounds do cause deaths. Many autopsy reports were obtained with the diagnosis of acute yellow atrophy of unknown cause, while on the cases on which autopsies were not performed, several diagnoses were made, such as cirrhosis, acute yellow atrophy, acute hepatitis, acute catarrhal jaundice, and carcinoma. Several clinical histories were studied in which the patient died in a comatose state shortly after admission to the hospital. The necropsy report was usually acute yellow atrophy of unknown cause. These cases could not be included because of the lack of a proper history. Only in rare instances was a history obtained of the previous use of any drug, and the time factor which may elapse between the use of cinchophen and the appearance of symptoms, could be easily overlooked. All of this confusion, vagueness of symptoms, and lack of knowledge that cinchophen was toxic, explain to a certain degree the scarcity of reports of fatalities from the use of this drug.

In studying the reports of cinchophen poisoning as seen in humans, we cannot escape the conclusion that there must be conditions beyond control. The question has arisen, is the toxicity of cinchophen and its compounds limited to human beings? Reproduction of cinchophen toxicity in animals has not been accomplished to the complete satisfaction of all observers; in general, the results have been negative.

Many clinicians are unanimous in their belief that cinchophen compounds are definitely toxic to the liver, but how this is brought about is a mystery. Many theories have been brought forth which will not be discussed here. Several contend that allergy offers a satisfactory explanation, while others contend that the abnormal susceptibility theory is most rational. The proponents of the latter theory believe that cinchophen in the presence of certain predisposing conditions may sensitize or otherwise damage liver cells in such a way as to produce yellow atrophy. Among these predisposing conditions mentioned have been chronic infectious biliary tract disease, cirrhosis, pregnancy, chronic alcoholism, nephritis, low-carbohydrate diets, and surgical procedures.

Review of Cases. The accompanying table presents a brief analysis of 32 cases, including 6 reported by the author, all of which appear to illustrate the phenomenon of acquired sensitivity, or susceptibility of cinchophen (phenylcinchonic acid) and its compounds.

Summary. 1. Thirty-two cases of cinchophen poisoning are reported including 6 by the author, which appear to illustrate the

TABLE 1.—CASES OF CINCHOPHEN POISONING.

Cutaneous Group.

Case No	Reference	Drug and dose.	Total dose.	Symptomatology.	Result.
1	Marañon 1914	A. at irreg. intervals	Unknown	No symp. during this treatment	Recovered.
		A. at later date	Unknown (small)	Itching, chills, fever depression, eruption on neck and arms	
2	Marañon 1914	A. irreg.	Unknown	No symps. during first treatment	Recovered.
		A. at later date	Unknown, said to be small	Itching, chills, fever, rash	
3	[illegible] 1929	C. on and off 5 or 6 times daily for several years	Unknown	No symps. during this period	Autopsy: Liver weighed 1950 gm. Spleen enlarged; yellow atrophy present.
		C. 80 tablets in 1 mo., 40 tablets of oxyliodide 1 mo. and C.	Probably 400 gr. 40 gr. 60 gr.	Jaundice with recovery Fever, diarrhea, nausea, vomiting, bleeding from nose and gums, skin rash and death in coma	
4	[illegible] 1924	C. gr. 15 at irreg. intervals	Probably 200 gr.	No symps. over long period, then collapse for ½ hr. cyanosis; recovery	Recovered.
		C. 2 tablets 3 mos. later	10 gr.	Collapse again, pink rash appeared on arms, face and chin	
5	David 1932 (Case 1)	N. 45 gr. daily for 10 days	505 gr.	No symptoms	
		N.	30 gr.	Rash on skin and rise in temp.	Recovered when drug was stopped.
6	David 1932 (Case 2)	C. over 1 mo.	1200 gr.	No symps. except nausea at the end of this time	Recovered when drug was stopped.
		N. 2 mos.	1800 gr.	Urticaria after 1 month later,	Recovered when drug was stopped.
		N.	10 gr.	severe urticaria	
		N.	5 gr.	One week later, rash developed	
7	[illegible] 1933	L. 30 gr. daily for 6 mos.	5400 gr.	No symptoms	Recovered.
		oxyliodide later	69 gr.	No symptoms	Patient reacted with increasing sensitivity.
		oxyliodide 3 mos. later	3 gr.	Chills, fever, itching and severe urticaria	
			Farastan	7.5 gr. cyanosis and urticaria	
		C.	7.5 gr.	Generalized urticaria	
8	[illegible]	C. intermittently for 1 year	Unknown	No symps. until about 12th month after beginning drug. Itching, nausea, vomiting, which cleared up Later erythema, vomiting edema, death	Autopsy: Liver presented gross, and histologic evidence of g. b., bile duct and panc. dis.
9	[illegible]	C., dose unknown	Unknown	No symps. at first. Later g.-i. symps., urticaria. Acquired sensitivity	Recovered.
10	[illegible]	A. [illegible] gr. t.i.d.	200 gr. 1933	No symptoms	Recovery after drug was stopped. Acquired sensitivity did not develop until 3rd year.
		A. [illegible] gr. t.i.d.	210 gr. 1934	No symptoms	
		A.	315 gr. 1935	No symptoms	
		A. gr. [illegible] days	20 gr. later	Generalized itching and rash over body	

A. = [illegible] C. = Cinchophen. L. = [illegible] F. = Farastan. N. = Neocinchophen.

TABLE 1.—*Continued*

Hepatic Group.

Case No.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Result.
11	deRezende[22] 1927	A. 5 gr. caps. t.i.d. 3 to 4 wks.	270 gr.	No symptoms	
		A. taken at later date	Unknown	Jaundice, duration 1 mo.	Recovered.
12	Rake,[19] 1927	A. indef. period	1500 gr.	No symps. for a long period. Then ac. abd. pain and jaundice	Autopsy: Liver weighed 1150 gm.
		A. gr. 10 over 2 days	10 gr.	Diag: Gallstones. Later diarrhea and vomiting recurred. Exploration, no gallstones found. Death 3 days later	Necrosis and regeneration.
13	Glover,[6] 1926	Atophanyl. Occasional intravenous injection	38.5 cc.	No app. di. arose until last series of treatments when there was evidence of liver damage	Recovered.
14	Loewenthal, Mackay, and Lowe,[11] 1928	A., 1.5 gm. daily for 6 mos.	3600 gr.	No evidence of poisoning until end of period, with jaundice, acute liver damage and death	Autopsy: Liver weighed 538 gm. Acute toxic necrosis.
15	Reichle,[21] 1929	C.	31,150 gr. in 1926	No symptoms	Autopsy: Liver weighed 757 gm.
		C.	21,100 gr. in 1927	No symptoms	Diagnosis: Yellow atrophy.
		C.	1800 gr. 1928	Epigastric pain, tenderness, weakness, jaundice, confusion, twitchings, convulsions, death	
16	Evans and Spence,[4] 1929	C., 5 to 6 gr. doses at irreg. intervals for 3 yrs.	Unknown	No symps. appeared until end of this time when he lost weight, with dizziness, weakness of legs, rapid heart. No skin rash	Recovered. All symptoms disappeared when drug was stopped.
17	Tak,[25] 1930	A.	150 gr.	No symptoms	Recovered 6 wks. later.
		A. at later date	45 gr.	Anorexia, enlargement of liver and jaundice	
18	Rabinowitz,[8] 1930	C., 10 gr. at irreg. intervals for 2 mos.	Probably 200 gr.	No symps. until at end of 2 mos. period; then jaundice and itching	Recovered after illness of 2 mos.
19	Ross,[23] 1931	T., several courses of treatment	Unknown	No symps. until final course of treat. followed by pain, vomiting, fever, jaundice, delirium, ascites, death	Autopsy: Liver weighed 670 gm. with necrosis of hepatic cells and evidences of regen.
20	Walker,[26] 1931	C., over long period	750 gr.	No symptoms	Autopsy: Liver weighed 650 gm. Hepatic cells showed evidence of necrosis and regen.
		C., 7½ gr. t.i.d.	125 gr.	Heartburn, nausea, jaundice vomiting, incr. in size of liver, delirium, death	
21	Parsons and Harding,[16] 1932	Rentons Hydracine tablets for 6 mos.	1000 gr.	No app. symps. until end of this period. Epigastric distress, vomiting, gradually deepening jaundice, death	Autopsy: Liver weighed 750 gm. and was necrotic.
22	Reah,[20] 1923	C., 7 gr. t.i.d. for 2 weeks;	About 300 gr.	No symptoms	Necropsy revealed red atrophy of the liver.
		1 mo. later a 2d course over 2 weeks	300 gr.	Shortly after the 2d course, nausea, anorexia, jaundice, death	
23	Weir and Comfort,[27] 1933	A.	500 gr.	No symptoms until end of period; then toxic cirrhosis	Recovery when these drugs were stopped and a high carbohydrate diet given.
		C., over 2 yrs.	500 gr.		
24	Perkel,[17] 1933	A., in 4 days	100 gr.	No symptoms	Autopsy: Liver weighed 400 gm.
		C., 2 mos. later over 9-day period	200 gr.	Symps. of liver damage, jaundice, death	Diagnosis: toxic necrosis.
25	Bloch and Rosenberg,[2] 1934	T. 7 to 15 gr. daily for 18 mos.	3000 gr.	No symps. until the end of period; then vague symps. of toxicity (no jaundice), death	Autopsy: Liver weighed 1250 gm. and toxic cirrhosis was present.

TABLE 1.—*Continued*

Case No.	Reference.	Drug and dose	Total dose.	Symptomatology.	Result.
26	Palmer, Woodall and Wang[13]	C in unknown amounts for indefinite period Later 24 tablets	Unknown 180 gr.	No symptoms Evidence of liver damage, death. No jaundice	Autopsy: Liver weighed 1051 gm.; acute toxic cirrhosis.
27	Bloch and Rosenberg,[3] 1934	Novatophan 10 gr. daily June, 1932	75 gr.	No symptoms	Autopsy: Liver weighed 700 gm.; yellowish-green, subacute necrosis.
		No treat. for 3 mos.	125 gr. for next 3 mos.	Weakness, nausea, vomiting, loss in wt. light colored stools. Death 2 mos. later. No jaundice	
28	Sugg, 1932 (Case 2)	A., gr. 5, t.i d. for 14 days Nov., 1931	200 gr.	Had taken A. for years at irreg. intervals with no toxic effects, until Nov., 1931; then jaundice, loss of appetite and wt. and clay-colored stools	All symptoms disappeared when drug was stopped.
		A., Jan., 1932	Unknown	Second attack of jaundice following A.	Recovered 6 wks. later after all A. was stopped
29	Sugg, 1933 (Case 3)	A., at intervals for years, Jan., 1933	Unknown	No symptoms during this period	
		A.	Unknown	Jaundice, clay-colored stools, nausea	Recovered.
		A., 6 tablets within 2 wks	20 gr.	Nausea, weakness, jaundice, fluid in abdomen. In hosp. 4 mos.	Recovered.
30	Sugg, 1934 (Case 4)	A. for several years	Unknown	No symptoms during this period	Liver: Ac. yellow atrophy.
		A., May, 1934	Unknown	Deep jaundice and extreme illness, death	
31	Sugg, 1935 (Case 5)	A., for 2 or more yrs., irreg.	125 gr. early part of 1934, 250 gr. 4 mos. later	No symptoms No symptoms	Recovered after ac. illness of 6 wks. duration. No harmful effects occurred until 3rd course.
		A., 10 gr. daily for 10 days, in March, 1935	100 gr.	Loss of appetite, weakness, jaundice, generalized itching, liver became large and tender	
32	Sugg, 1935 (Case 6)	A., for several years, irreg.	Unknown	No symptoms	
		A. for 3 wks. in 1934	75 gr.	No symptoms	
		A., 5 gr. doses for 1 mo., 1935	Between 75 and 100 gr.	Jaundice in 2 wks. after drug was begun. Deepened, and was followed by weakness, loss of wt., itching, bile in urine, clay-colored stools. Abd. distended, liver big and tender	Recovered after ac. illness of 3 mos. Liver not normal in size until 1 yr. later.

phenomenon of an acquired sensitivity or susceptibility to this drug. The case histories of other observers as well as my reports are divided into two groups: 1, A cutaneous group of 10 cases with 2 deaths; 2, a hepatic group of 22 cases with 12 deaths.

2. Many theories have been advanced as to the exact cause of the toxicity of cinchophen, only 2 of which are discussed here: (*a*) That the necrosis of the liver which almost invariably results, is due to an abnormal susceptibility of the individual because of certain predisposing conditions; (*b*) that the various toxic manifestations of cinchophen are allergic in nature.

3. An individual may not show toxic symptoms from the use of cinchophen upon its first administration, nevertheless, damage may have occurred which may be accentuated by readministration, even after several months or years.

4. The mechanism of acquired sensitivity from non-protein substances, such as cinchophen, is not understood. Landsteiner and others believe that an antigen antibody mechanism explains hypersensitivity, though it is unproven.

5. Reports of toxic cirrhosis definitely attributed to cinchophen are increasing. The relationship between this drug and liver damage was not understood until recent years, even in the presence of jaundice, and toxic cirrhosis without jaundice was not appreciated at all.

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A COMPARISON OF INTRACUTANEOUS REACTIONS IN MAN TO THE PURIFIED PROTEIN DERIVATIVES OF SEVERAL SPECIES OF ACID-FAST BACTERIA.*

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The specificity of the tuberculin reaction in man is seldom questioned. Krause[11] in 1916 concluded: "it would appear that there

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* This work was supported in part by a grant from the Wisconsin Alumni Research Foundation and is published with the permission of the Director of the Wisconsin Agricultural Experiment Station.

is no cutaneous hypersensitiveness without a focus (tubercle)." And Hart,[8] in 1932, in a monograph on the tuberculin test says: "and if the words 'under natural conditions' are added, and possible cross-reactions within the species are excepted, this (Krause's) view is held by most workers today."

On the other hand, the specificity of the tuberculin reaction in cattle has been questioned, because the percentage of tuberculin-reacting cattle showing no macroscopic lesions of tuberculosis upon autopsy has steadily increased, and because the percentage of such animals in all the cattle tested has remained practically constant, as the program for the eradication of tuberculosis in cattle has progressed. In 1922 in the United States 8.7% of the cattle reacting to the intracutaneous test showed no macroscopic lesions of tuberculosis. And in 1936 in Wisconsin of 2343 reacting cattle, 33% showed no macroscopic lesions and 12% showed skin lesions only. Crawford[5] concludes that the majority of these no-visible-lesion tuberculin-reacting cattle in the United States have microscopic lesions of tuberculosis, but that some may be infected with human or avian tubercle bacilli. The etiology of the skin lesions is unknown; microscopically acid-fast organisms are found in the lesions, but tubercle bacilli cannot be cultivated therefrom, and many workers believe that acid-fast bacteria from the soil are the causative agents.

In Wisconsin, Hastings and co-workers[9] recovered saprophytic acid-fast bacteria from the lymph nodes of no-visible-lesion tuberculin-reacting cattle, and by injecting massive doses of these organisms succeeded in sensitizing non-tuberculous cattle to tuberculin. Hastings and co-workers[10] isolated avian tubercle bacilli from the lymph nodes of a no-visible-lesion tuberculin-reacting cow, and McCarter, Hastings, and Beach[14] isolated avian tubercle bacilli from the lymph nodes of 3 out of 28 tuberculin-reacting cattle showing minimal lesions of tuberculosis.

Since, then, cross reactions within the genus of acid-fast bacteria are responsible for the non-specificity of some reactions to mammalian tuberculin in cattle, such cross reactions might also be responsible for some reactions to mammalian tuberculin in man. The failure of some 80% of University of Wisconsin students reacting to tuberculin to show either healed or active tuberculous lesions upon chest x-ray indicates the possibility of sensitization by some agent other than the human or bovine tubercle bacillus. Undoubtedly a few of these individuals have extra-pulmonary tuberculous lesions, and presumably the majority of them have pulmonary lesions which either are very small or have healed and left no traces, because pathologists will admit that in many autopsies minimal lesions of tuberculosis are missed. Conceivably, some of these minimal tuberculous lesions in man may be caused by some species of acid-fast bacteria commonly considered non-pathogenic for man.

The survey reported here on the comparative testing of university students with the purified protein derivatives (P.P.D.'s) of the human and of the avian tubercle bacillus and of *Mycobacterium smegmatici* was made to find whether these other mycobacteria were responsible for the sensitization of some individuals to human tuberculin.

Tests with avian tuberculin have been reported. Seibert and Morley[19] using P.P.D.'s, tuberculins standardized as to the weight of active principle present, showed a quantitative specificity in the reactions of tuberculous guinea-pigs to human and avian tuberculins. The results of Fenger and co-workers[7] in testing man with an avian MA100 tuberculin (another chemically standardized tuberculin first prepared by Masucci and McAlpine[15]) also suggested that human and avian tuberculins might be quantitatively, if not qualitatively, specific for sensitization by the homologous organism; but the method used by these workers was not designed to investigate the specificity of the tuberculin reaction. The results of the comparative testing of man with human and avian Old Tuberculins reported by Dolgopol[6] and Branch[4] are invalidated because of a combination of two factors: O.T.'s vary widely in their content of active principle and cross reactions to avian tuberculin occur in humans sensitized by mammalian tubercle bacilli.

In this study we were concerned primarily with sensitization to tuberculin by the avian tubercle bacillus as it might affect reactions to mammalian tuberculin, rather than with the production of manifest disease by the avian type. Sensitization to tuberculin could be caused by the presence of avian tubercle bacilli in the body, even if they did not produce detectable disease. The organisms might enter the body through the intestinal tract by the ingestion of infected eggs or through the respiratory tract by breathing contaminated dust.

We have considered also one other factor which might be responsible for tuberculin reactions in individuals never infected with human or bovine tubercle bacilli; namely, sensitization by tuberculin itself. Seibert[18a] has found the human P.P.D. to be nonsensitizing for guinea pigs. Aronson and Nicholas[2] have reported sensitization of man by the MA100 tuberculin, the second injections being given 3 months after the first. Steele and Willis[21] have found that by giving repeated injections of tuberculin at intervals of 2 days, practically all children can be sensitized to tuberculin. The small amount of work which has been done indicates that the average size of the molecules in the particular tuberculin used may determine its power to sensitize.

Technique. *Purified Protein Derivatives.* The human, bovine, and avian tuberculins used were the purified protein derivatives kindly supplied us by Dr. Seibert of the Phipps Institute. The protein derivative of *Mycobacterium smegmatici* was prepared for us by Seibert's method through the courtesy of Dr. Reichel of the Mulford Biological Laboratories of Sharp and

Dohme. The human Old Tuberculin came from the Saranac Lake Laboratory. The tuberculins were all diluted from the stock solutions by one of the authors, using chemically clean glassware, and pipettes rather than syringes.

Dosage and Injection. The standard doses of P.P.D. prescribed by Long, Aronson, and Seibert[13] were used throughout. Of O.T. the weak dose was 0.01 mg. and the strong dose 1.0 mg. The human P.P.D. and the P.P.D. to be compared therewith were injected simultaneously by different operators one in each forearm. The volume given was standardized by the size of the bleb raised. "Sterile" needles were used for each student, the needles for each P P.D. being separately "sterilized" in boiling water throughout the day.

Reading of Reactions. The standards of Aronson[1] were used in grading the reactions. An edema of less than 5 mm. in diameter, or erythema of more than about 10 mm. in diameter was noted on the records, but for statistical purposes such reactions were called negative

Chest Roentgenograms. The chest x-rays were single anteroposterior films taken by the X-ray Department of the Wisconsin General Hospital, and were read independently by 2 individuals.

Selection for Statistics. In compiling our statistics, we used only the data on those students who were from 18 to 23 years of age, and who reported on schedule so that their reactions could be read about the 48th hour.

Experimental. *A. Avian P.P. D.* Comparative tests with human and avian P.P.D.'s were made on two unselected groups of 500 Freshman men each. Similar comparative tests were made on one

TABLE I.—REACTIONS OF UNIVERSITY MALE STUDENTS TO HUMAN AND AVIAN P.P D.'S AND FINDINGS OF CHEST X-RAYS OF POSITIVE REACTORS.

Number and group of students	Reactions to P.P.D.'s.	%	Chest x-rays. No.*	Group.† 1 (%).	2 (%).	3 (%).	4 (%).
730 Freshman	Human + and Avian +	23 8	172	68 0	23.8	6 4	1.8
	Human + and Avian −	0 4	3	66.7	0	33 3	0
	Human − and Avian +	22 3	161	90 7	8 1	1 2	0
	Human − and Avian −	53 5	0				
125 Agricultural Short Course (Farm)	Human + and Avian +	21 6	27	74 1	25 9	0	0
	Human + and Avian −	0 8	1	100 0	0	0	0
	Human − and Avian +	33 6	0				
	Human − and Avian −	44.0	0				
162 Agricultural Short Course [illegible]	Avian +	53 7	82	92 7	6 1	1.2	0
	Avian −	46 3	0				

* Some students failed to report for x-rays and so the number of x-rays will not agree in all cases with the number of reactors.

† Chest x-ray groups:

1. No pathologic changes, or some evidence of previous disease of questionable etiology, e. g., adhesions, thickened trunks, etc.; or organized deposits which may be calcium but nature questionable.
2. Calcified Ghon tubercle, hilum nodes, or both (primary tuberculosis).
3. Infiltration with questioned activity (activity can be proved only by extended study of the patient).
4. Active adult tuberculosis (activity proved by detailed laboratory and clinical study of the patient).

unselected group of Agricultural Short Course students,* and tests with avian tuberculin only on another unselected group of Short Course students, since it was thought that the two tuberculins given simultaneously might be acting as a stronger dose of one of the tuberculins and causing more reactions. Chest x-rays were taken of all positive reactors (except on the reactors to avian in one group of farmers). The results of the tests and the x-ray findings are placed in Table 1, the results on the two Freshman groups being combined because the differences were not significant.

Three phenomena are brought out in Table 1: 1, with the exception of 3 students, all students reacting to human tuberculin also reacted to avian; 2, a relatively large number of students reacted to avian and not to human, the percentage of such reactors being greater in the Short Course group than in the Freshman group; and, 3, some of the students who reacted to avian and not to human showed calcified lesions of tuberculosis upon x-ray. Thus, the results were unexpected and their significance is not self-evident. Therefore, our interpretation of them will be reserved for the discussion on all the data.

The results on testing the Short Course students with avian P.P.D. only showed that probably one dose of tuberculin injected alone elicits the same reaction as when 2 doses of tuberculin are given simultaneously on opposite arms, since the total percentage of Short Course students reacting to avian P.P.D. in the one group was not significantly different from the total percentage reacting in the second group.

The tabular data give only a comparison of the qualitative reactions to avian and human tuberculins, but quantitative relationships were also observed. The strong reactors we shall arbitrarily call those who react to the first dose or who react 3+ or 4+ to the larger dose, and the weak reactors those who react 1 or 2+ to the larger dose. We found that *all* strong reactors to human P.P.D. reacted less to avian P.P.D., while the weak reactors to human reacted in the same degree to avian, that is, all individuals reacting strongly to avian P.P.D. were more sensitive to human P.P.D. The significance of these data also will be discussed later.

Two control groups of x-rays were obtained on a part of the students who reacted to neither human nor avian P.P.D. The combined results on the two groups in Table 2 show that none of these students had healed or active tuberculous lesions; the x-ray of one individual showed an infiltration similar to the infiltrations of early tuberculosis, but the diagnosis could not be confirmed because the student failed to report for further examination. So that according to Tables 1 and 2, all individuals with calcified lesions reacted to avian tuberculin.

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* All Agricultural Short Course students come from farms.

TABLE 2.—FINDINGS ON THE CHEST X-RAYS OF MALE STUDENTS WITH NEGATIVE REACTIONS TO BOTH HUMAN AND AVIAN P.P.D.

		Chest x-ray group.			
Group of students.	No.	1 (%).	2 (%).	3 (%).	4 (%).
Freshman	153	98.7	0.6*	0.6†	0

* This student showed on the test with avian tuberculin erythema and edema 3 mm. in diameter.

† This student failed to report for further examination and, therefore, the progress of this lesion has never been checked.

In addition to testing university students with avian tuberculin, we did attempt to test families on farms where the flocks of chickens were badly infected with avian tubercle bacilli. We visited the farms personally, but so much time was required in influencing the farmers to take the test, that it was impossible, without undue expenditure of time and money, to carry out a significant number of tests.

B. Bovine P.P.D. and Smegmatici P.P.D. The P.P.D. from the bovine tubercle bacillus and the P.P.D. from *M. smegmatici* were compared with human P.P.D. in the same way as the avian was. An unselected group of Freshman men in September, 1936, were tested with human and bovine P.P.D.'s, and another unselected group with human and smegmatici P.P.D.'s. Chest x-rays were taken on all positive reactors except that funds were not available for films of those individuals reacting to smegmatici and not to human (Table 3). In their qualitative relationships the human and bovine P.P.D.'s are seen to be almost comparable, although about 5% of the students reacted to human and not to bovine, and 0.5% to bovine and not to human. The qualitative relationships of the reactions to human and smegmatici P.P.D.'s differed both from those to bovine and those to avian; some students reacted to smegmatici and not to human P.P.D., but the percentage

TABLE 3. REACTIONS OF UNIVERSITY MALE STUDENTS TO HUMAN AND BOVINE AND TO HUMAN AND SMEGMATICI P.P.D.'S AND FINDINGS ON THE CHEST X-RAYS OF THE POSITIVE REACTORS.

			Chest x-rays.				
				Group.			
Number and group of students.	Reactions to P.P.D.'s.	(%).	No.	1 (%).	2 (%).	3 (%).	4 (%).
391 Freshman	H + and B +	25.1	97	61.9	33.0	2.1	0
	H + and B −	4.6	16	87.5	12.5	0	0
	H − and B +	0.5	2	0	100.0	0	0
	H − and B −	69.8	0				
541 Freshman	H + and S +	11.0	60	88.3	11.7	0	0
	H + and S −	6.0	28	67.9	21.4	7.1	3.6
	H − and S +	9.9	2	50.0	50.0	0	0
	H − and S −	70.1	0				

H = human. B = bovine. S = smegmatici.

was only about half that of those reacting to avian and not to human; and a small but significant percentage reacted to human and not to smegmatici, whereas the number of students reacting to human and not to avian was insignificant.

In comparing the size of reactions to human and bovine P.P.D.'s we found that the reactions were consistently very nearly of the same intensity, some of the reactions to bovine being 4 or 5 mm. larger in diameter than those to human, and other reactions being slightly greater to the human. Furthermore, those individuals who reacted to human and not to bovine were all weak reactors, giving only 1+ reactions to the strong dose. Thus, according to these data, human and bovine P.P.D.'s are of about equal potency, the human being slightly more potent than the bovine for man, and therefore these tuberculins could not be used to distinguish between infections with human and bovine tubercle bacilli. This has been assumed to be true in the testing of cattle since human tuberculin is used almost exclusively for this purpose.

The quantitative relationships of the reactions to smegmatici with those to human P.P.D. were somewhat like those to avian P.P.D. All those individuals who were strong reactors to human reacted less to smegmatici and every individual who gave a strong reaction to smegmatici gave a stronger reaction to human. And again all students who reacted to smegmatici but not to human gave only 1 or 2+ reactions to the large dose. On the other hand, of those who reacted to human and not to smegmatici half reacted to the weak dose and half reacted to the strong dose.

C. Salt Solution Controls. Since the difficulty of removing tuberculin from syringes has been emphasized by Nelson, Seibert, and Long,[17] an unselected group of male students were used as a control group and given injections of 0.85% sodium chloride solution as well as of human P.P.D. Eighteen of the 460 tested reacted to "salt solution." That these reactions were due to contamination of the syringes with tuberculin was proved by reinjecting some of these same students 6 months later using new (unused) syringes and needles. The reactions to NaCl occurred in very strong reactors to tuberculin, all these students being sensitive to the small dose, and the reactions were much smaller to the NaCl than to the tuberculin. These facts, together with the fact that the number of reactors was small, cause us to conclude that contamination with human tuberculin could not have been responsible for the consistent occurrence of cross-reactions to avian and bovine P.P.D.'s in individuals sensitive to human P.P.D. It is possible but not probable that all the cross-reactions to smegmatici P.P.D. were due to contamination of the syringes with human P.P.D., since some students who reacted to human did not react to smegmatici. And, of course, none of the other data could be questioned on this basis, since reactions to the other P.P.D.'s in individuals not sensitive to human

P.P.D. could not have been caused by contamination with human P.P.D.

D. Sensitization by Tuberculin to Tuberculin. The human and avian P.P.D.'s as well as a sample of O.T. were tested for their sensitizing abilities by re-injecting students 6 months after the original test. This period of time was chosen since it is the interval between retests recommended by the Student Health Committee of the National Tuberculosis Association.[23]

So that O.T. could be compared with P.P.D. in its sensitizing potency, an unselected group of 500 Freshman women had been tested with O.T. and 23% found to react.

One group of Freshmen who had been negative to avian P.P.D. were called for a retest with avian P.P.D. 6 months later. Freshmen in the second group who had been tested with avian, and all those who had been tested with bovine or smegmatici P.P.D.'s, and who had not reacted to *human* P.P.D., were retested 6 months later with human P.P.D. The Freshmen women who had not reacted to Human O.T. 6 months before were retested with O.T. diluted from the same batch of concentrated tuberculin. These results are all included in Table 4.

TABLE 4. REACTIONS UPON RETESTS WITH HUMAN AND AVIAN P.P.D.'S AND HUMAN O.T. 6 MONTHS AFTER THE ORIGINAL TEST.

Tuberculin used for retest.	Reactions to original test.	Number retested.	Reactions upon retest. Pos. (%).	Reactions upon retest. Neg. (%).
Avian P.P.D. . .	Human − and Avian −	137	33.5	66.4
Human P.P.D. .	Human − and Avian +	44	31.8	68.2
	Human − and Avian −	86	4.6*	95.4
	Total Human −	130	13.8	86.2
Bovine P.P.D.	Human − and Bovine +	1	100.0	0
	Human − and Bovine −	132	6.1	93.9
	Total Human −	133	6.8	93.2
Human P.P.D.	Human − and *Smegmatici* +	21	4.8	95.2
	Human − and *Smegmatici* −	174	4.0	96.0
	Total Human −	195	4.1	95.9
Human O.T.	Human O.T. −	201	10.4	89.6

* These include all who showed on the original test to avian P.P.D. an erythema greater than 10 mm. in diameter but only slight edema (less than 5 mm. in diameter).

All the reactors positive to the test with human tuberculin were *x*-rayed, but the *x*-ray findings are not tabulated because the films showed no evidence of either healed or active tuberculosis. X-rays were not obtained on those reacting to the retest with avian P.P.D.

The number of students reacting to the retest with avian P.P.D. was surprisingly large: 46 out of 137 (about ⅓), had become positive reactors within 6 months. These reactions were almost certainly caused by sensitization by the tuberculin itself, because it seems unreasonable that sensitization was caused by infection with any type of tubercle bacillus.

On the other hand, the human P.P.D. does not sensitize according to the following evidence. In the avian group all who reacted to the retest with human P.P.D. had shown some sensitivity to *avian* P.P.D. 6 months before, although a few of these individuals had had reactions with too small an area of edema to be called positive. This observation, together with the fact that no lesions of tuberculosis were found on the x-rays of the reactors to the retests, means that the original injection of avian tuberculin increased an already existing sensitivity in these individuals so that they reacted upon a second injection of human P.P.D. This also means that those individuals in the bovine and smegmatici groups who reacted upon the retest to human P.P.D. would have reacted 6 months before to avian P.P.D. The percentage of reactors upon retest with human P.P.D. in the bovine and smegmatici groups is about the same, an average of about 5% for the two groups, while the percentage of reactors in the avian group is over twice as great. Statistical analysis showed the difference to be significant, and proves that the "population" in the avian group is different from the "population" in the combined bovine and smegmatici groups. The only experimental variable in the two groups is that one was injected with avian tuberculin, and therefore the conclusion is that the avian tuberculin is more potent than human or bovine or smegmatici P.P.D. in increasing the slight sensitivity of individuals who do not give reactions upon the first injection of human tuberculin.

The percentage of reactors to the retest with O.T. is slightly greater than the percentage of reactors to the retest with human P.P.D. in the bovine and smegmatici groups. However, with the comparatively small numbers of persons examined, the difference is not sufficiently great to be statistically significant, so that we cannot conclude that the O.T. is more potent in increasing sensitivity than the human P.P.D.

As a further test of sensitization by O.T., the reactions to human tuberculin were compared in the Freshmen who had had tuberculin tests in high school in the last year and in those who had never had such tests. No correlation was found, the percentage of reactors to the university test being about the same in both groups. Of course, very few of the students had had more than one test in high school, and probably only a weak dose of 0.01 or 0.1 mg. of O.T. had been used. With the tests now given annually, some effect may be found in the future.

E. Significance of Erythematous Reactions. According to the present standards, reactions with less than 5 mm. of edema are called negative even though considerable erythema may be present. We have taken chest x-rays of 17 women, all of whom had reactions which would be called negative but had erythema of more than 10 mm. in diameter. The x-rays of 3 of these individuals showed calcified lesions of tuberculosis. Also as noted above, such substandard reactions to avian P.P.D. indicated some sensitization to tuberculin as shown by reactions upon retest. A phase of erythema with no edema was observed by Mote and Jones[16] as the initial stage in experimental skin sensitization to serum protein, the edema appearing later; the sensitization disappeared in opposite order, erythematous reactions being the last evidence. Erythematous reactions, which are too large to have been induced by the needle prick, are, then, probably evidence of sensitization to tuberculin.

Discussion. *A. Specificity of Purified Protein Derivatives from Different Species of Acid-fast Bacteria.* We attempted to find whether human beings might be sensitized to human tuberculin by acid-fast bacteria other than the human or bovine tubercle bacillus, by making comparative tests on university students with the purified protein derivative tuberculins of the avian tubercle bacillus and of the smegma bacillus. We found that we could not solve our problem by this method, because the reactions to these protein derivatives could not be explained on the basis of our present knowledge of tuberculin and of the tuberculin reaction.

The reactions to avian and smegmatici tuberculins in persons with strong reactions to human tuberculin can be explained as cross reactions, because they were all less in degree than the reactions to human. These quantitative relations in the reactions to avian and smegmatici tuberculins show that these protein derivatives are not so closely similar to the human protein derivative as that of the bovine tubercle bacillus, since the severity of the reactions to bovine P.P.D. was of the same degree as that of the reactions to human in the same individuals.

On the other hand, the reactions to avian and smegmatici in weak reactors, or in non-reactors, to human P.P.D. cannot be explained with our present knowledge. The following evidence is against the explanation that these reactions are specific, *i. e.*, that they are due to sensitization by the avian tubercle bacillus or by the smegma bacillus:

1. The consistency in the quantitative relations of reactions to human and to avian or smegmatici P.P.D.'s disappears in the group of individuals reacting only 1 or 2+ to the strong dose of human P.P.D.; these all react in about the same degree to the avian or to the smegmatici as to the human.

2. The number of individuals reacting to avian P.P.D. and not to human is relatively large, and these reactions are all weak, being only 1 or 2+ to the strong dose.

3. The reactions to avian P.P.D. in individuals not sensitive to human P.P.D. cannot be correlated with rural residence of these individuals. About 70% of such individuals live in cities with populations of over 2500.

4. The evidence all points to a difference in the antigenicity of the human P.P.D. and of the avian P.P.D. Our experimental evidence for this is that one injection of avian P.P.D. sensitized one-third of the individuals tested to a second injection of the same substance, whereas human P.P.D. does not sensitize. This difference in antigenicity may be that the avian P. P. D. consists of molecules of larger average size than those of the human P.P.D., since Seibert[18b] has shown that the size of the molecule determines whether or not various tuberculins will sensitize experimental animals. And Aronson and Nicholas[2] have demonstrated the sensitization of human beings by the human MA100 tuberculin which has a higher molecular weight than the human P.P.D. tuberculin. Confirmatory evidence to this hypothesis is also given by the work of Barnwell and Pollard[3] on University of Michigan students. They found by using the human T.P.T. (the protein precipitated by trichloracetic acid) tuberculin, which also has a higher molecular weight than the human P.P.D. tuberculin, about the same percentage of reactors as we did by using the avian P.P.D. Also they found almost twice as many reactors with the human T.P.T. as with human O.T., whereas we found about twice as many reactors to avian P.P.D. as to human P.P.D. Barnwell and Pollard state that T.P.T. tuberculin does not sensitize but we should like to question this interpretation of their results. They found by giving 7 or more tests to students and nurses over a period of from 1 to 20 months that 27 of the total of 46 became positive. Is not such a percentage of reactors upon retest rather high to assign to infection with tubercle bacilli within a period of 20 months?

According to our hypothesis the human and avian P.P.D.'s are quantitatively specific in highly sensitive individuals, but less sensitive individuals react in the same degree to avian as to human because of the greater antigenicity of the avian. The slightly sensitive individuals who react to avian P.P.D. but not to human P.P.D. may have been sensitized by the human tubercle bacillus, but the human P.P.D. cannot elicit a reaction whereas the avian P.P.D. can by virtue of its greater antigenicity. Such reactors may also have been sensitized by the avian tubercle bacillus, and our data on the students from farms, the Agricultural Short Course boys, show that this probably occurs. A combination of the data gives a total of about 54% of 287 agricultural students reacting to avian and of about 46% of 739 Freshmen, and upon statistical analysis it proves to be very probable that this difference is significant.

In making the P.P.D. tuberculins the protein molecules are hydrolyzed in the process of concentration by heat and probably also in the process of precipitation by trichloracetic acid. Therefore no exact control is exercised over the degree of degradation of the protein, and differences in the nature of the proteins of the various species of acid-fast bacteria might well account for the differences in the size of the particles in the tuberculins.

B. The Specificity of the Tuberculin Reaction. The qualitative specificity of the tuberculin reaction must be questioned; we cannot prove with our present knowledge that all reactions to human P.P.D. are due to sensitization by the human or bovine tubercle bacillus, and we know that some individuals with healed lesions of tuberculosis do not react to human P.P.D. We cannot prove that individuals with weak reactions to human P.P.D., *i. e.*, 1+ or 2+ to the strong dose of 0.005 mg., have been sensitized by the human or bovine tubercle bacillus, because such individuals react in about the same degree to the P.P.D.'s of other acid-fast bacteria such as the avian tubercle bacillus and the smegma bacillus. On the other hand, those individuals whose chest *x*-rays show healed lesions of tuberculosis, but who react only to avian and not to human P.P.D., have most probably been sensitized by mammalian tubercle bacilli. But again, that all the reactions to avian P.P.D. in individuals not reacting to human P.P.D. are due to sensitization by mammalian tubercle bacilli has not been proved. Sensitization by other acid-fast bacteria may be responsible for some of the reactions to human P.P.D. and to avian P.P.D. It seems likely that such sensitization may be responsible because acid-fast organisms are omnipresent, occurring both on the membranes of man and in the soil; and because the similarity of the protein derivatives of such acid-fast bacteria as the avian tubercle bacillus, the smegma bacillus, and the phlei bacillus, to the protein derivatives of the human and bovine tubercle bacillus is shown by cross-reactions in man and other animals.

Of course, non-bacterial proteins or proteins of bacteria in other genera may be so related to the proteins of acid-fast bacteria as to produce sensitization to tuberculin. Selter and Tancre[20] found that tuberculous individuals reacted to peptone and casein and to an extract of the cells of *Escherichia coli*. Their solutions of these products may have been contaminated with tuberculin since Nelson, Seibert, and Long[17] found that tuberculin could be removed from syringes and other glassware only by treatment with alkali or dichromate solution. Therefore Selter and Tancre's work is open to criticism and would have to be repeated under rigid control before acceptance.

The tuberculin reaction is quantitatively specific, because all those with active cases of tuberculosis react to human P.P.D. and because all strong reactors to human P.P.D. react less to avian or to smegmatic P.P.D. Barnwell and Pollard[3] found that all individuals with active tuberculosis with one exception reacted to human O.T. and we found with one exception that all students with active tuberculosis reacted to human P.P.D. The exceptional case of the former authors was one of skin tuberculosis and our case[22] was one of atypical tuberculosis of the lymph nodes; Barnwell and Pollard's patient reacted to human T.P.T. and ours reacted to avian P.P.D. Students whose chest roentgenograms show lesions of questionable activity do sometimes fail to react to human P.P.D., as can be seen from our tabular data, but all such students whose lesions were later proved to be pathologically active* had reacted to human P.P.D. on the original test.

The conception of the tuberculin reaction as being beyond question qualitatively specific was formed because O.T. was used by all workers. According to the graph of Hart[8] where the percentage of reactions in a "normal" population is plotted against the strength of dose of O.T. given, increases in the doses of O.T. above 10 mg. detect very few reactors. But Barnwell and Pollard's[3] graph shows that plotting the percentage of reactors to human T.P.T. against the dose given results in a straight line curve, the percentage of reactors increasing almost proportionally with the dose of T.P.T. given; and the percentage of reactors to the strongest dose of T.P.T., 0.01 mg., being almost twice as great as the percentage of reactors to a dose of 1.0 mg. of O.T. Of course, one cannot reason by extrapolation that if still larger doses of T.P.T. were given, 100% of the population would react, and no experimental data are available on this point. Apparently the difference which accounts for the larger number of reactors to the T.P.T. tuberculin is that this product has a higher molecular weight than the O.T.

The validity of our explanation for the lack of qualitative specificity of the tuberculin reaction cannot be proved until the nature of the difference between the human and the avian P.P.D. is found by chemical methods, and until further evidence is adduced on the effect of the size of the molecule of the antigen upon skin hypersensitivity. There are no observations on the effect of the size of the molecule upon skin reactions in humans or laboratory animals with varying degrees of sensitivity. In fact, very little is known concerning the antigenic nature of protein hydrolysis products even for the precipitin reaction (see Landsteiner,[12] p. 132).

C. The Use of the Tuberculin Test. Our results change our program for controlling tuberculosis in the student body very little, but they give us a sure basis for that program. The tuberculin test with human P.P.D. or with human O.T. remains valuable as an aid to the diagnosis of active cases of tuberculosis. At this University where but 30% of the entering students react to human P.P.D., the active cases can be discovered by the use of the tuberculin test and by chest *x*-rays of the positive reactors, at less than half the cost of *x*-rays only on all the students. In cases where a patient who has a lesion suspected to be of tuberculous origin fails to react to human P.P.D. or to human O.T., tests with human T.P.T. or with avian P.P.D. should be made before the diagnosis of tuberculosis is questioned. The adoption of human T.P.T. or of avian P.P.D. for routine testing would not be desirable because the possibilities of sensitization by the tuberculins themselves are so great. Testing with avian P.P.D. does find all those who have healed lesions of tuberculosis as well as those with active lesions, but progressive lesions very seldom develop in these individuals with calcified lesions in the experience of one of the authors (R. H. S.). Again some individuals with healed lesions give sub-standard reactions to human P.P.D. and the physician will have to use his own judgment as to whether the cost of *x*-rays on all individuals with sub-standard reactions is justified by the finding of some calcified lesions. Intervals of 6 months between retests with human P.P.D. are sufficient to preclude possible sensitization by human P.P.D. according to our results; according to the results of Steele and Willis[21] short intervals between retests may not preclude sensitization. The value of tuberculin tests of negative reactors at intervals of 6 months should be questioned; of 458 students retested with human P.P.D. after 6 months, 35 reacted and none of them showed either healed or active lesions upon *x*-ray. Probably, retests at intervals of 1 year are sufficient. The great majority of those students who give positive reactions 6 months after giving negative reactions have not been infected with tubercle bacilli, but merely their sensitization to tuberculin has been increased by the initial injection of tuberculin, because *all* the students in the avian group who reacted upon retest with human P.P.D. in February, 1937, had been sensitive to avian P.P.D. in September, 1936.

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* The "pathologically active" cases include those which are not clinically active; the activity in such cases was proved by laboratory study.

On the other hand, the percentage of reactions to human P.P.D. or to human O.T. can no longer be used as an accurate measure of the extent of infection of the population with tubercle bacilli. Thus, we have no method of estimating the number of individuals who have or have had infection with tubercle bacilli, because we do not know the significance of reactions to human T.P.T. or to avian P.P.D. tuberculin in individuals who do not react to human P.P.D. or O.T.

Conclusions. 1. Intracutaneous reactions to the purified protein derivatives (P.P.D.'s) of the various acid-fast bacteria are not qualitatively specific.

2. The bovine P.P.D. is very similar in nature to the human P.P.D.

3. The avian and smegmatici P.P.D.'s differ from the human P.P.D. in nature and also in antigenicity.

4. Under the conditions of our experiment, avian P.P.D. has sensitized man while human P.P.D. has not, although one injection of human P.P.D. will increase an already existing slight sensitivity.

5. Almost 100% of the students with active tuberculosis react to human P.P.D. All students with calcified tuberculous lesions

react to avian P.P.D., but some of them fail to react to human P.P.D.

6. The tuberculin test is useful in a public health program for the detection of active cases of tuberculosis in a large group such as the university student body, because it can be used to select those who should have chest *x*-rays. But it should be used as an indication rather than as an exact measure of the extent of infection with tubercle bacilli in the general population, because not all individuals with healed or active tuberculous lesions react to human P.P.D. or O.T., and because we cannot prove that all individuals who react to human P.P.D. or O.T. have been sensitized by the human or bovine tubercle bacillus. Some reactors may have been sensitized by other mycobacteria commonly considered non-pathogenic for man.

7. More knowledge of the chemistry of the various tuberculins will materially aid in the interpretation of reactions to these tuberculins.

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THE COMPOSITION OF HUMAN BONE IN CHRONIC FLUORIDE POISONING.

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The toxic effects of fluorides on experimental animals are well known.[6,13] In contrast, there are few extensive data on man, although many instances of acute poisoning by soluble fluorides are recorded.[14, 16a, 20] Until recently only 1 case of chronic poisoning, attributed to fluorides in beer, has been reported.[19a] There is, however, a well-known relationship between the amount of fluorides in drinking water and the incidence of mottled enamel or chronic endemic dental fluorosis.[5] In this condition both bones and teeth showed a marked increase in fluorine content.[4] Factory workers exposed to cryolite dust showed extensive skeletal changes characterized by massive sclerosis of the bone and increased opacity to Roentgen rays.[15] In 2 of these workers who came to necropsy the bones were chalky white and abnormally large, showed extensive sclerosis, and gave an ash which contained a maximum of 1.31% fluorine.[16b, c]

The present report deals with the composition of bone from a case of chronic fluoride poisoning in man. Except for the fluorine content, the analytical data show essentially normal ratios for all constituents studied. Complete Roentgen ray studies, clinical observations and necropsy findings on this patient have been reported.[2, 3]

Materials. The patient, a negro, male, aged 48, under treatment for luetic heart disease, had been exposed almost daily for 18 years to finely ground rock phosphate dust containing 3.88% fluorine. A Roentgen ray examination revealed, in addition to cardiac enlargement, very intense shadows of the bones in the trunk, osteophytes on the vertebral column, a thickened pelvic girdle and some calcification in the attachments of the ligaments.[3]

The bones (described in detail with illustrations elsewhere[2]) were thicker and heavier than normal. The external surfaces were covered with chalky white areas, nodular or platelike exostoses and osteophytes. A portion of isolated rib appeared much more opaque to Roentgen rays than did a normal rib of the same external dimensions (Fig. 1). In cross-section the fluoride rib showed an abnormally thick cortex and very prominent trabeculæ. The teeth were very brittle, but were free from any markings characteristic of mottled enamel.

The bones removed at necropsy were defatted and dried by successive extraction with purified ethyl alcohol and anhydrous ether and finally ground to a powder which passed a standard 80-mesh sieve.

Analytical Methods. Bone samples were ignited in the electric muffle furnace for 5 hours at 670° C. and the weight of the ash obtained. Each sample of ash was dissolved in a small amount of normal HCl acid and after adjustment to pH 3.5, the calcium was precipitated and weighed as the oxalate.[2] For the colorimetric phosphate determination[7] bone ash was dissolved in normal HCl and digested at 100° C. for 10 minutes. Fluorine in the bone ash was distilled from perchloric acid[17] and determined by titration with thorium nitrate in the presence of alizarin.[1] Carbon dioxide determinations on dry fat-free bone were made by the manometric procedure using the details given by Shear and Kramer.[22]

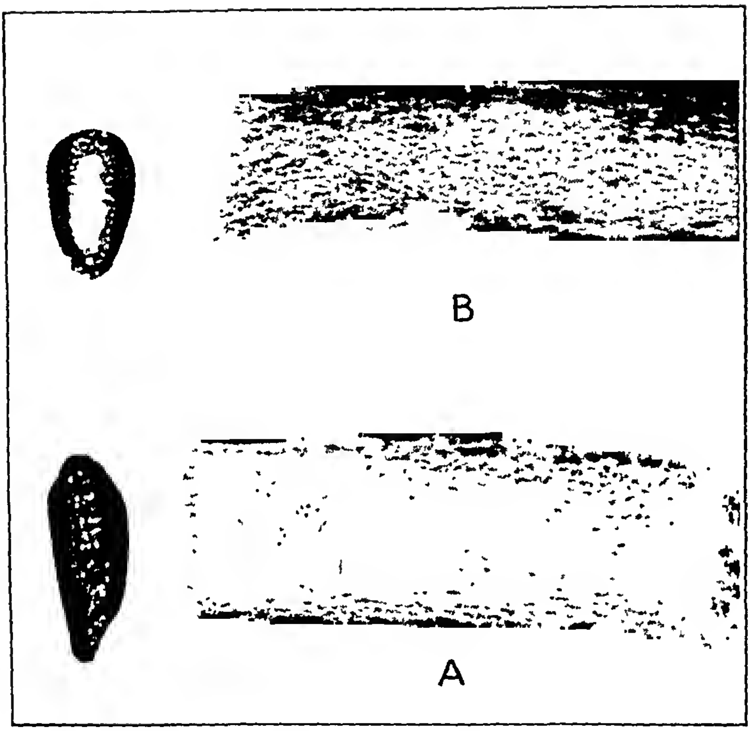

FIG. 1.—Roentgenogram showing; (*A*) increased opacity to Roentgen rays and increased wall thickness of the rib in chronic fluoride poisoning as compared to the (*B*) normal rib.

Control analyses on normal bone gave satisfactory values. Standard fluorspar gave 46.21% fluorine (theory 46.15%). Phosphate rock used by the plant in which the patient worked averaged 3.88% fluorine in a series of 7 determinations.

Specific gravity determinations were made in the usual manner by weighing bone sections in air and in water, but it was necessary to soak the bones for 24 to 48 hours before making the second weighing. Results are referred to distilled water at 25° C.

TABLE 1.—THE COMPOSITION OF HUMAN BONE IN A CASE OF CHRONIC FLUORIDE POISONING. (RESULTS AS PER CENT OF DRY FAT-FREE BONE.)

Bone.	Ash (%).	Calcium (%).	Phosphorus (%).	Fluorine (%).	Carbon dioxide. (%).
Femur, mid shaft, cortex*	66.47	29.37	11.60	0.29	4.19
Tibia, mid shaft, cortex	65.01	29.32	11.44	0.18	4.16
Ulna, mid shaft, cortex	65.51	29.27	11.67	0.22	4.28
Skull, frontal section	64.19	29.01	11.37	0.38	4.22
Rib, sixth, cross section	66.84	29.24	11.51	0.56	4.25
Sternum, manubrium	64.52	27.51	11.21	0.69	3.93
Vertebra, body of lumbar	65.38	29.01	11.37	0.70	4.14
Vertebral cortex	63.44	.....	.....	0.68	
Osteophyte, vertebral	.....	.....	.....	0.66	
Teeth	74.95	.....	.....	0.10	

* Analytical data expressed as weight per unit volume of bone would be 3.6% below normal values because of the low specific gravity.

Results. Analytical data presented in Table 1 show essentially normal values for ash, calcium, phosphorus, and carbon dioxide. The fluorine content of these bones ranges up to 20 times the values usually considered normal.[6,10,12,13] The results indicate that fluorides accumulated to a greater extent in the softer bones, sternum, ribs and vertebral column, than in the long bones. However, the latter show a fluorine content many times the normal value.

Specific gravity determinations were made on cortical sections of the femurs as removed at necropsy. Results (25°/25°) were as follows: Normal femur A, specific gravity 1.902; normal femur B, 1.903; fluoride femur, 1.833. Similar differences were found in specific gravities of the dry fat-free femurs. Specific gravities of the ribs could not be determined with any degree of accuracy, probably because of air occluded in the spongy structure.

Discussion.—An outstanding characteristic of chronic fluoride poisoning either in man or animal is the accumulation of fluorine in the bones. Values for the fluorine content of bones in our case are comparable to the figures reported for similar studies by others.[4,11,16b,c,21] The same concentrations of fluorine in the body of the vertebra, its cortex and an adjacent osteophyte suggest a state of dynamic equilibrium in this bone. The ratio of fluorine to other constituents is the same whether old bone structure (vertebra) is being recalcified or new bone (osteophyte) formed. Probably the smaller amount of fluorine in the long bones indicates a less mobile equilibrium in these areas as compared with the vertebra.

The fact that we found normal values for carbon dioxide suggests that the fluorine was deposited as a calcium or magnesium fluoride. Had fluorine entered the crystal to form fluorapatite an equivalent quantity of carbon dioxide should have been displaced. (See studies on carbonate apatite structure of bone.[9,17,24])

Normal figures for calcium and phosphorus suggest that no great disturbance occurred in the mechanism of calcification. Fluorides in small doses over long periods of time apparently stimulate a widespread growth of bone. Although this affected bone is unusually opaque to Roentgen rays, actually it has an abnormally low specific gravity and is, therefore, less dense than normal bone. The increased opacity to Roentgen rays may be attributed to the presence of more bone substance rather than to any increase in the actual density of the bone (Fig. 1).

In certain respects chronic fluoride poisoning in man duplicates that observed in experimental animals. The enlarged chalky white bones with numerous exostoses found in our case and the 2 cases reported by Roholm,[16b,c] are similar to the bony changes which occur in pigs receiving fluorides.[11] These gross physical abnormalities occur in bones with little change in composition. Similar observations have been made on rats.[18] The increased opacity of the bones to Roentgen rays, so prominent in man, has been noted, to a slight degree, in rats,[16d,23] but not in dogs.[8,*] A decrease in the specific gravity of bone in man is duplicated by a similar decrease in the rabbit.[16b] Other similarities have been discussed extensively by Roholm.[16a]

Summary. Human bones from a case of chronic fluoride poisoning contained normal percentages of calcium, phosphorus and carbon dioxide. The fluorine content was increased up to 20 fold the normal value and unequally distributed in various parts of the skeleton, highest in the vertebra and lowest in the long bones. The specific gravity of the femur was low. Data on man and animals are compared.

The authors are indebted to Dr. John T. Bauer for invaluable advice throughout the course of this work, and to Dr. Paul A. Bishop for collaboration, especially for [illegible] Fig. 1.

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* [illegible] dogs show bone changes detectable by [illegible] identical with those in man.

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PURULENT TYPHOID MENINGITIS WITH RECOVERY.

CASE REPORT.

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MENINGEAL infection due to Bacillus typhosus is a rare complication of typhoid fever; its occurrence in the absence of clinical typhoid fever is exceedingly unusual; recovery from it apparently unheard of.

The subject has been reviewed most recently by Bayne-Jones[2] and Baumgartner and Osen.[1] Prior to 1920, 27 unequivocal cases of purulent typhoid meningitis had been reported. Since then 23 cases have appeared in the literature. All cases of purulent typhoid meningitis thus far reported have been fatal. Meningitis associated with typhoid infections has been divided into 3 types: 1, meningismus or the occurrence of meningeal signs in the absence of any meningeal lesions, *i. e.*, a non-specific toxic reaction; 2, serous meningitis, in which there are symptoms of meningitis with lymphocytosis in the spinal fluid and actual bacterial invasion, edema of brain, round-cell infiltration and a serous exudate; 3, purulent meningitis, *i. e.*, showing predominance of neutrophils in the spinal fluid as well as positive cultures for B. typhosus. This form of meningitis is quite often preceded by the serous form. It has been noted by Baumgartner and Osen[1] and Fernet[3] that cases of typhoid meningitis usually have a minimal enteritis or other common lesions of typhoid fever.

Case Report. CASE L. L. (A-65213).—A 42-year-old white male was admitted to this hospital on March 28, 1936 (twenty-sixth day of disease) because of chills, fever, headache, drowsiness and photophobia. On March 2, 1936 (first day of disease), after an alcoholic debauch, patient suffered a sudden, severe, shaking chill, felt feverish and developed severe headache and marked anorexia. On the fourth day of the disease projectile vomiting was noted in addition to the above symptoms. The neck was stiff but lumbar puncture was refused. Vomiting subsided on the sixth day of the disease but chills and fever persisted. Because of persistent meningeal signs, patient was sent to a hospital on the ninth day of disease. Lumbar puncture afforded considerable temporary relief from the headache but chills and fever persisted. On the nineteenth day the patient left the hospital against advice. Between the twentieth and twenty-fourth days patient was at home having persistent headache, chills and fever. Drowsiness and photophobia also developed during this time. Spinal fluid was grossly cloudy on the twenty-sixth day of disease when the patient was sent to this hospital.

Past history was irrelevant. Patient had never had typhoid fever and had never been vaccinated for typhoid.

Examination revealed a middle-aged Polish male, both acutely and seriously ill. Pupils were equal and reacted normally. External ocular movements were normal. Optic disks were normal. Stiff neck, bilateral Kernig and positive Brudzinski signs were noted. Moderate dullness with suppression of breath and voice sounds was noted at the right base. No râles were heard. Heart was essentially normal. Spleen was not palpable. No rose spots were seen. Reflexes were physiological.

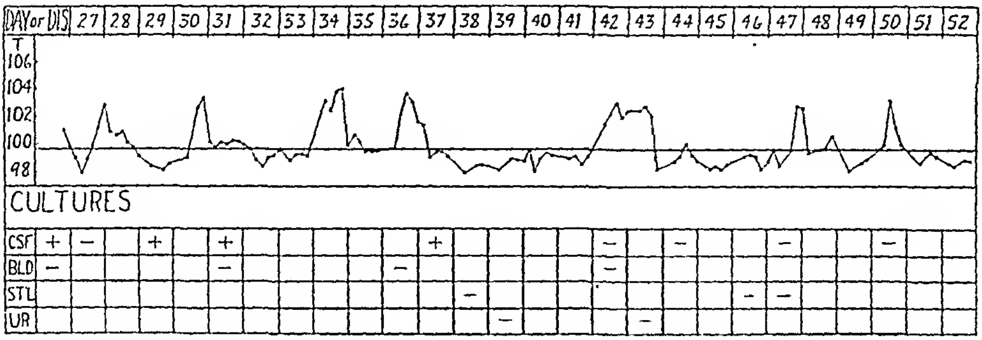
Laboratory Data (Table 1). Kahn test was negative. Urine was normal.

TABLE 1.—LABORATORY DATA.

	Spinal fluid						Cultures.				Serologic data.			
Day of disease	Pressure	Pandy	Appearance	Cell count, (% polys)	Smear	Culture.	Blood.	Bile.	Stool.	Urine.	Widal, blood.	Widal, C.S.F.	Pt's. ser. vs. pt's. org.	Pt's. C.S.F. vs. pt's. org.
9		4+	Clear	800 (30)	Neg									
11		4+		1200 (2)	Neg.				...	.	Neg.			
17		4+	Cloudy	1200 (2)	Neg	Neg.								
22*	250	4+	Purulent	3420 (73)	Neg	Gram neg. rods. Diphtheroids	Neg.							
27	160	4+	Turbid w. shreds	750 (50)	Neg.	Neg.								
29	185	4+	Cloudy	386 (22)	Neg	Gram neg. rods								
31	170	4+	Ground glass w. shreds	1100 (60)	Neg	Gram neg. rods	Neg.							
[illegible]							Neg.	. .	...	...	Neg.			
[illegible]	60	4+	Ground glass	1030 (64)	Neg.	Gram neg. rods								
[illegible]								.	...	...	...	..	Neg.	
[illegible]						..	.	.	B. coli					
[illegible]	[illegible]	4+	Ground glass w. shreds	[illegible] (70)	Neg.	No growth	Neg.	.	...	Neg.				
[illegible]														
[illegible]	[illegible]	4+	Ground glass	[illegible]		No growth	.	.	. .	Neg.				
[illegible]								...	B. coli					
[illegible]	[illegible]	4+	Clear	[illegible]		No growth	.	...	B. coli				Neg.	
[illegible]	[illegible]	4+	Ground glass w. [illegible]	[illegible] (32)		No growth		...	...	...	.	...	...	Neg.
[illegible]	[illegible]	4+	Clear	[illegible]		Slight †			B. coli					
[illegible]	[illegible]	4+	Clear	[illegible]		No growth								
[illegible]														
[illegible]	[illegible]		Clear	[illegible]		No growth		Slight						
[illegible]							.		...	...	Neg.	..		Neg
								Neg	..	.	.	Neg.		

* [illegible] New Haven Hospital. † Colony count.

Throughout the febrile period the leukocyte count ranged from 9300 to 16,700 with 74 to 93% neutrophils. Stools were normal, with negative guaiac and microscopic examinations. Cultures of nasopharynx showed the normal flora on two occasions. Roentgen ray of chest showed questionable bronchiectasis at right base.



DAY or DIS		27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
CSF	+	−		+		+						+					−		−			−			−		
BLD	−					−					−						−										
STL													−								−	−					
UR														−				−									

FIG. 1.—Purulent typhoid meningitis with recovery: Case report.

Course. Patient ran an intermittent fever (Fig. 1) for 3½ weeks after admission to the hospital. Febrile periods accompanied by severe headache and increased meningeal irritation usually came on at 3- to 4-day intervals. Treatment was symptomatic. Lumbar punctures were done as often as seemed indicated.

Result. Patient's spinal fluid was sterile after the thirty-seventh day of disease (twelfth day of hospitalization). Thereafter clinical improvement was definite, although fever persisted through the fiftieth day. Patient was discharged from the hospital on May 7, 1936 (sixty-sixth day of disease), apparently in good health. Six months later was again seen and interval history was negative and physical examination revealed the persistence of abnormal physical signs at the right lung base. There were no abnormal neurologic findings. General condition was excellent.

Bacteriology. Results of the bacteriologic investigations of the Gram-negative rod isolated on 4 occasions from the spinal fluid of the patient reported are presented in Tables 2 and 3.

The organism was a Gram-negative rod occurring at first as a highly pleomorphic organism, showing short fat bacilli, "blown up" coccus forms, diplobacilli and long thin rods. After several transplants on standard agar (pH 7.4), the morphology became uniform, the majority of the forms being short Gram-negative rods. On eosin-methylene blue agar, after 48 hours at 37° C., the colonies were raised, smooth, glistening and entire, measuring 1 to 3 mm. in diameter. The colonies had a bluish tinge with reflected light and blue centers with transmitted light. On Krumwiede's triple sugar medium, as well as Russell's medium, an acid butt without gas and an alkaline slant were produced. The organism was motile.

The characteristic biochemical reactions of B. typhosus as presented in Topley and Wilson (1936)[4] were present (Table 2). There is practically complete agreement between the results obtained both in the medical bacteriology laboratory of this hospital and those of the Connecticut State Laboratory* and Topley and Wilson's text.

Serologic evidence presented in Table 3 leaves little doubt of the organism's identity. It will be noted that the organism failed to agglutinate when first isolated, but after several transplants the reaction occurred in significant dilutions.

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* To Mr. Friend Lee Mickle, Connecticut State Department of Health, the author is indebted for his interest and coöperation in obtaining the complete bacteriologic data of this organism.

TABLE 2. BIOCHEMICAL REACTIONS OF SPINAL FLUID ORGANISM.

	New Haven Hospital.	Connecticut State Laboratory.	Topley and Wilson (1936).
Dextrose	A	A	A
Lactose	–	–	–
Mannite	A	A	A
Maltose	A	A	A
Sucrose	–	–	..‡
Salicin	–	–	..
Dextrin	A	..	A
Rhamnose	–	–	–
Raffinose	–	–	..
Inosite	–	–	–
Inulin	–	..	..
Dulcite	–	–	±*
Arabinose	–	A	±
Cellobiose	..	–	..
Xylose	..	–	±
Sorbite	..	A	A
Galactose	..	A	..
Adonite	..	–	..
Citrate	..	–	..
Voges-Proskauer	..	–	..
Methyl red	..	+	..
Nitrate	..	+	..
Indol	..	–	..
Gelatin	..	–	..
Litmus milk	..	Sl. ac.	Ac. or neut.
Lead acetate	..	–	+
Glycerol	..	–	–

* Variable or delayed fermentation. ‡ .. test not done.

TABLE 3. SEROLOGIC REACTIONS OF SPINAL FLUID ORGANISM.

Test.	Result.
Patient's organism vs. typhoid serum (New Haven Hosp.)	–
Patient's organism vs. typhoid serum (Conn. State Lab.)	1:5000 1:320 1:2560 1:10240 (H) 1:10240 (O) 1:640 (vi)
Patient's organism vs. *B. paratyphosus* A serum.	–
Patient's organism vs. *B. paratyphosus* B serum.	–
Patient's organism vs. *B. abortus* serum	–
Patient's organism vs. meningococcus serum	–

Comment. There are several unusual features in this case worthy of mention. Outstanding is the fact that clinical typhoid fever was never present or at least never recognized in this patient. In addition, the onset was fairly typical of meningitis and stiff neck was observed as early as the fourth day of the disease, suggesting that this represents a primary typhoid meningitis. The organism was isolated from the spinal fluid only. Agglutinins for stock strains of B. typhosus or his own organism could never be demonstrated either in blood serum or spinal fluid. Perhaps even more unusual is the fact that the patient recovered.

Summary. A case of purulent typhoid meningitis with recovery is presented.

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INFLUENCE OF SEASON AND CLIMATE ON THE MORTALITY OF THE WHITE AND COLORED POPULATION FROM TUBERCULOSIS AND THE ACUTE RESPIRATORY INFECTIONS.

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If, as is commonly believed, negroes are ill-adapted to withstand the rigors of colder climates, it would seem not improbable that this fact is due in large part to the influence of respiratory diseases. Not only is mortality from these diseases higher in winter than in summer, but there is evidence that it is higher in cold than in warm climates, although the influence of season is much greater than that of latitude. If cold enhances the mortality from respiratory diseases more in negroes than in whites, it might be regarded as playing a principal part in determining the present geographic distribution of the two races.

In studying this question an obvious procedure would be to compare the respiratory death rates of the two races in different climatic areas. In the United States the value of such a comparison, however, is reduced by the fact that northern and southern negroes live under different conditions and differ in education, economic status, age composition, and the admixture of white blood. Besides, the northern negroes are largely urban, whereas southern negroes are mainly rural. Hence it is not evident to what extent the differences in mortality of northern and southern negroes are due to climate and to what extent they result from the various other factors I have mentioned.

For this reason it occurred to me that some pertinent information might be gained by studying the seasonal trend of the respiratory death rate in the two races within the same geographic regions. With the aim of securing a large amount of statistical data on the subject, I have compiled the number of deaths from respiratory diseases and tuberculosis occurring in each month of the year in 9 states: namely, Tennessee, Maryland, North Carolina, South Carolina, Mississippi, Louisiana, Florida, Kentucky, and Virginia. These states were chosen because they have a large negro population and because separate tables for the white and colored inhabitants are available in the volumes on mortality statistics over the entire 10-year period covered, which extended from January 1, 1921, to December 31, 1930. The area includes approximately one-half of the whole negro population of the United States. Although data are not available for negroes as distinct from other colored races, the colored population of these states consists of over 99% of negroes. In the calculations of monthly death rates the number of deaths in each month was adjusted to a month of constant length. The populations exposed to death in the several months were calculated as of the 15th of each month on the basis of an assumed constant rate of increase during the period.

The study brought out the striking fact that although the respiratory death rate for both races varied greatly with season, the variations were much less in the colored than in the white population. In such a study one may easily be betrayed, on account of variations of disease incidence, combined with variations in the proportions of the two races in different areas. Hence, in order to guard against any statistical fallacy thus arising, I have also compared seasonal fluctuations in mortality in the two races within the limits of individual cities. In the few cities in which sufficient data are available, the month of lowest mortality from lobar pneumonia and bronchopneumonia in both races is July or August. The month of highest mortality tends to occur earlier in the South than in the North. In the cities of the South the most fatal month for respiratory diseases is usually January, as it is for the 9 states investigated, but it is more commonly March in the cities of the North. The death rate increases in September, and more rapidly in October, November, and December. For the sake of comparing the seasonal fluctuations in respiratory death rates in the white and colored populations, I have added the deaths in the 4 months of lowest mortality, usually June, July, August, and September, and have compared these with the 4 months of highest mortality, usually December, January, February, and March. In each of the large cities studied, the differences between summer and winter mortality from both lobar pneumonia and bronchopneumonia were greater in the white than in the colored population. The evidence that I have been able to secure indicates that the seasonal fluctuations in the respiratory death rate are greater in the whites than in the negroes in rural areas, as well as in cities and in the several states.

TABLE I.—RATIOS OF WINTER TO SUMMER MORTALITY FROM RESPIRATORY DISEASES IN THE WHITE AND COLORED POPULATIONS OF SELECTED NORTHERN AND SOUTHERN CITIES, 1921–1930, INCLUSIVE.

City.	Lobar pneumonia. White.	Lobar pneumonia. Colored.	Broncho-pneumonia. White.	Broncho-pneumonia. Colored.
Chicago	3.5	2.8	3.2	2.5
New York	3.8	3.6	2.9	2.4
Philadelphia	4.8	3.5	3.5	2.5
Baltimore	5.4	3.6	3.2	2.8
Atlanta	3.6	2.5	4.5	2.4
New Orleans	3.1	2.2	2.2	1.7

The relative fluctuations of the death rates of the two races from respiratory diseases are subject to considerable variation. In New York City the difference in degree of fluctuation is relatively small as compared with that which was found in other cities and states. In Mississippi, a state in which the population is mainly rural, the seasonal fluctuation is about the same in both races, and for lobar and undefined pneumonia is slightly, but perhaps not significantly, greater for the whites than for the colored population. In Alabama and Georgia, for the period before 1930 in which these states were in the Registration Area, and also Louisiana—states in which the vital statistics of white and colored people might be fairly comparable to those of Mississippi—the whites showed a greater seasonal fluctuation than the colored from both lobar and bronchopneumonia.

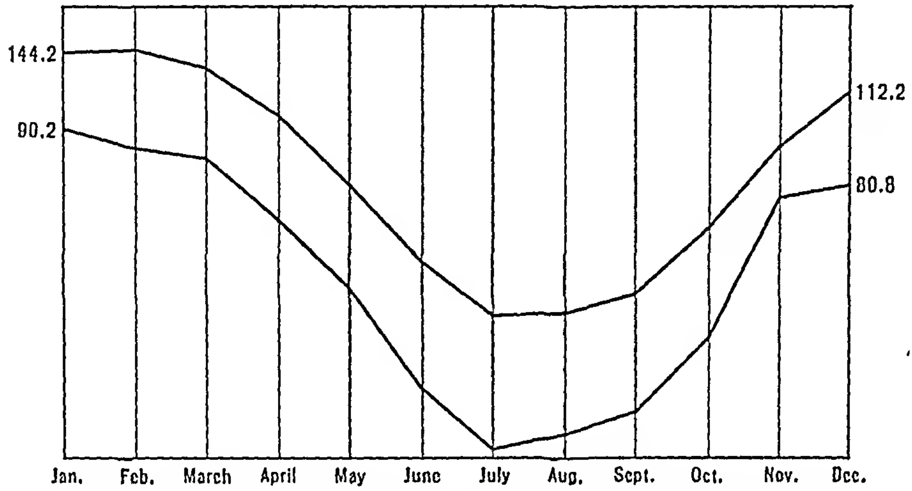

FIG. 1.—Death rates by month from pneumonia (lobar and undefined) in the white and colored population of 9 selected states, 1921–1930. This and the following graphs are drawn to a logarithmic scale in order better to represent changes in mortality rates. Mortality of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

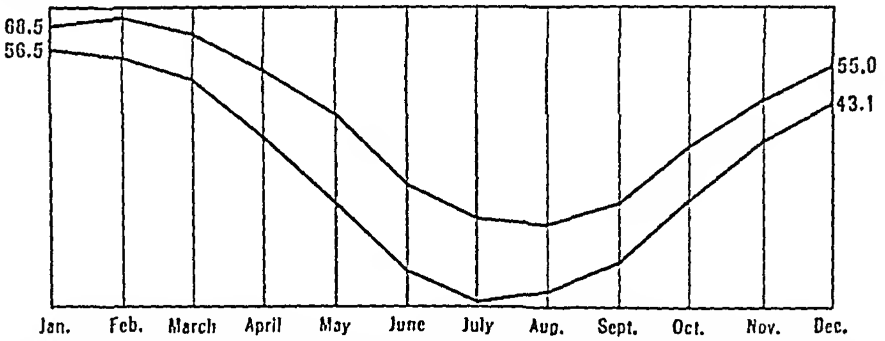

FIG. 2.—Death rates by month from bronchopneumonia in the white and colored population of 9 selected states, 1921–1930. Mortality rates of the colored represented by upper line, that of whites by lower line. Rates per 100,000.

There seems to be little relation between the death rate from pneumonia and the degree of its seasonal fluctuation. One finds marked seasonal fluctuations, as in Baltimore, associated with a high pneumonia death rate, and also marked seasonal fluctuation associated with low pneumonia death rate, as in Mississippi. Possibly the extent of seasonal fluctuation may be influenced by age composition, but in the absence of mortality rates by months in the several age groups it is not possible to secure definite information on this point.

TABLE 2. DEATHS BY MONTH AND DEATH RATES FROM RESPIRATORY DISEASES IN THE WHITE AND COLORED POPULATION OF 9 SELECTED STATES, 1921–1930.

	Pneumonia, lobar and undefined.				Bronchopneumonia.				Bronchitis.			
	Deaths.		Rates.		Deaths.		Rates.		Deaths.		Rates.	
	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.
January	9938	6582	90.2	111.2	6526	3125	59.3	68.5	786	424	7.14	9.30
February	8799	6700	79.8	146.9	6232	3309	56.5	72.5	806	410	7.31	8.99
March	8339	5981	75.5	131.0	5440	2982	49.3	65.3	722	407	6.54	8.91
April	5717	4462	51.7	97.7	3790	2365	34.3	51.8	552	317	4.99	6.95
May	3812	2971	31.4	65.0	2517	1812	22.7	39.7	395	281	3.56	6.16
June	2044	1819	18.5	39.7	1659	1168	15.0	25.6	298	239	2.69	5.23
July	1408	1320	12.7	28.8	1296	933	11.6	20.9	254	216	2.29	4.73
August	1549	1339	13.9	29.3	1471	922	13.2	20.2	273	217	2.46	4.75
September	1780	1507	16.0	32.9	1764	1050	15.8	22.9	328	223	2.95	4.87
October	2849	2229	26.6	48.6	2623	1510	23.5	33.0	498	282	4.48	6.16
November	5223	3699	58.8	80.8	3797	1991	34.1	43.6	586	317	5.24	6.92
December	7123	5141	63.7	112.2	4818	2518	43.1	55.0	608	327	5.45	7.14

TABLE 3. DEATHS AND DEATH RATES FROM INFLUENZA AND TUBERCULOSIS IN THE WHITE AND COLORED POPULATIONS OF 9 SELECTED STATES, 1921–1930.

	Influenza.				Pulmonary tuberculosis.				Tuberculosis, other forms.			
	Deaths.		Rates.		Deaths.		Rates.		Deaths.		Rates.	
	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.	W.	C.
January	14,424	6,958	130.9	152.5	8821	7557	80.0	165.7	886	697	8.04	15.29
February	10,011	6157	91.1	135.1	9033	8048	81.9	176.4	976	714	9.03	15.65
March	[illegible]	6122	87.5	134.2	9147	8456	82.8	185.3	1012	768	9.17	16.84
April	5,657	3810	51.1	84.1	8862	8772	80.2	192.1	1038	872	9.39	19.10
May	2,442	1851	22.2	40.6	7702	8615	69.6	188.6	992	942	8.96	20.62
June	1,001	917	9.0	20.0	7348	8154	66.3	178.4	980	897	8.84	19.61
July	[illegible]	551	5.4	12.0	6805	7762	61.3	169.8	992	815	8.94	18.41
August	[illegible]	411	3.2	9.0	6301	7179	56.7	157.0	878	785	7.90	17.17
September	750	547	6.8	12.0	6005	6371	54.0	139.3	877	703	7.88	15.36
October	[illegible]	[illegible]	11.9	18.2	6218	6528	55.8	142.6	861	701	7.73	15.38
November	2,512	[illegible]	22.8	39.2	6719	6630	60.2	141.8	815	605	7.30	13.21
December	[illegible]	[illegible]	55.7	74.9	6994	6658	62.6	145.4	809	608	7.24	13.27

In the area and 10-year period investigated, deaths from lobar pneumonia, bronchopneumonia, and bronchitis reached their highest rates in January or February, and their lowest rates in July or August. For bronchitis the ratio of deaths in the 4 months of lowest mortality to deaths in the 4 months of highest mortality is nearly 1:3 in the whites, and slightly less than 1:2 in the colored races (Table 2).

In the years studied, influenza, like other respiratory infections, is much more fatal in winter than in summer. Mortality in the cold months is about 9 times as high as in warm months in the colored, and over 13 times as high in the white race. The highest mortality for both races occurred in January, and the lowest in August. It is doubtful if this month of maximum mortality will be found to be of general occurrence. There is much variation in severity from year to year in all of the acute respiratory infections, but influenza is more fitful in its visitations than any of the others.

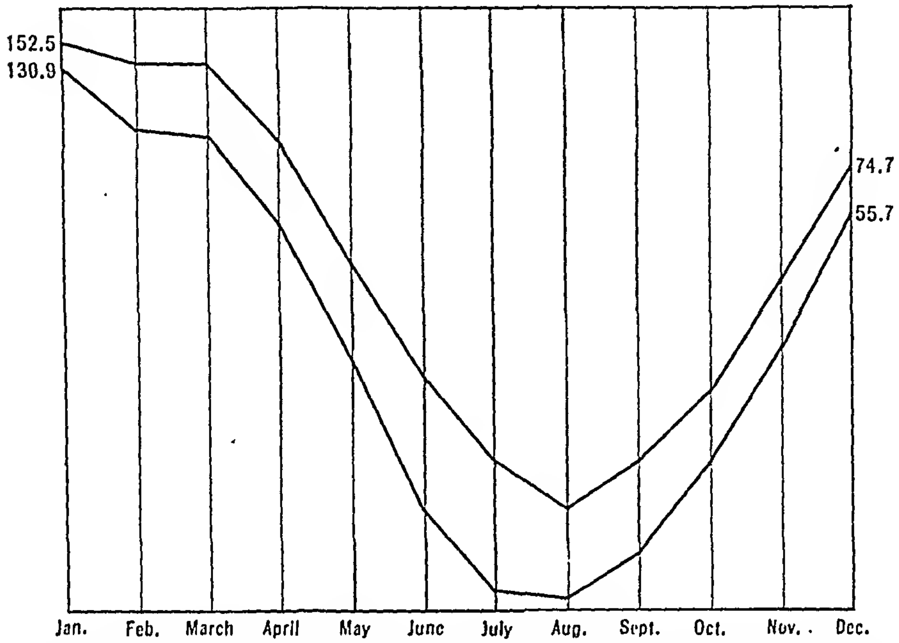

FIG. 3.—Death rates by month from influenza in the white and colored population of 9 selected states, 1921–1930. Mortality rates of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

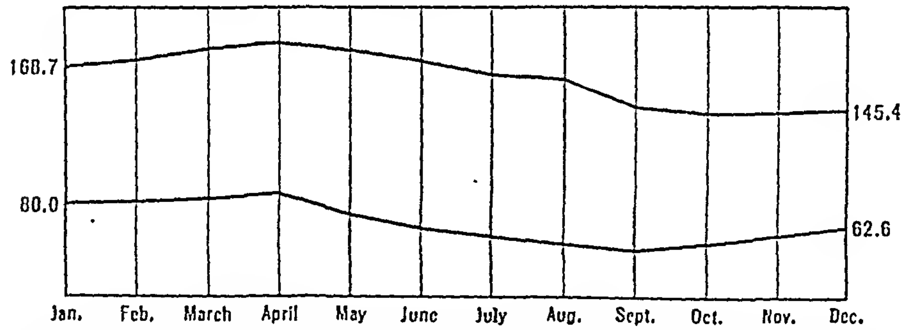

FIG. 4.—Death rates by month from pulmonary tuberculosis in the white and colored population of 9 selected states. Mortality of the colored shown by upper line, that of whites by lower line. Rates per 100,000.

The seasonal variations in mortality from pulmonary tuberculosis (Table 3) are in several respects parallel with those of the acute respiratory infections, but they show some differences which place tuberculosis in a somewhat different category. The highest mortality rates are scarcely more than 50% higher than the lowest ones, instead of several times as high, as in the pneumonias. The fluctuations in mortality from tuberculosis in the colored populations are closely parallel to those of the white and show about the same relative degree of seasonal change, although the death rate is a little over twice as high as in the white race. That the wave of highest mortality from tuberculosis which comes in April lags behind that of the acute respiratory infections may be due to the fact that people usually die from the latter diseases soon after they contract them, and that people are less apt to contract them in warm weather. Although tuberculous patients do not have so plentiful a supply of fresh air in winter as in summer, the higher mortality from tuberculosis in the colder months may be in part due to the acute respiratory infections which afford the immediate occasion of death. Many such deaths would be reported, and properly so, as due to tuberculosis. The seasonal distribution of "other forms of tuberculosis" differs from that of the respiratory forms in that the highest mortality in both the white and the colored populations occurs in the spring and early summer, and the lowest ratio in the fall and early winter.

Our data indicating that in the colored population mortality from respiratory diseases fluctuates less with the seasons than that of the white population might dispose one to infer that higher latitudes, while increasing the respiratory death rate in both whites and colored people, would lead to a greater relative increase in the mortality of the colored race. One cannot, however, safely argue from the effects of seasonal change to the effects of change of latitude. The lower seasonal fluctuations in mortality of the colored people may be due to the fact that for some reasons negroes are much more apt than whites to die from respiratory diseases in summer. I suspect that this is the case, but whatever may be the character or the course of the seasonal change in mortality from respiratory diseases in the two races, the change from rural life in the South to urban life in the North affects negroes very much more unfavorably than white people. Between the crude mortality rates from pneumonia in the rural South and in the rural North there is roughly an average difference of from 30 to 75% for the whites, and from 200 to 300% for the colored population. Possibly the destructive influence of negro migration into the North is due more to the fact that the migration is urban than that it involves life in a northern climate.

For light on this subject one would naturally turn to a comparison of the respiratory death rates of northern and southern urban negroes, but such a comparison reveals many irregularities and little relation to latitude. The death rate from pneumonia is high in the colored population of Atlanta, Chattanooga, Dallas, Baltimore, Richmond, and Washington, D. C. Relatively low rates from pneumonia occur in the colored inhabitants of Philadelphia, Chicago, and, especially, Gary. These variations, however, may be largely caused by differences in age composition, educational status, and the frequency of climatic changes in different cities.

TABLE 4.—PERCENTAGES OF TOTAL DEATHS DUE TO PNEUMONIA AND DEATH RATES PER 100,000 IN THE WHITE AND COLORED POPULATION OF RURAL AND URBAN AREAS OF SELECTED STATES, 1921–1929.

State.	Percentage of pneumonia to total mortality.				Mortality per 100,000.			
	White.		Colored.		White.		Colored.	
	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.
Illinois	7.80	7.58	12.12	7.22	82.7	63.4	216.5	222.5
New York	9.63	6.75	15.65	9.44	95.2	68.2	264.7	138.8
Pennsylvania	10.46	9.07	17.98	11.02	115.3	88.1	257.2	204.1
Ohio	7.83	6.84	14.23	7.53	113.9	84.8	287.7	160.0
Maryland	9.70	6.97	15.40	8.39	134.8	73.3	347.0	146.3
Virginia	5.96	6.42	10.05	6.53	76.8	64.9	232.1	112.6
South Carolina	5.89	7.16	7.57	6.99	102.0	61.5	229.6	99.4
Mississippi	6.08	7.24	6.50	6.27	121.9	66.4	184.0	78.9
Louisiana	6.08	7.77	9.01	7.06	83.3	48.9	209.2	83.7

But notwithstanding irregularities due to causes other than climate, the crude mortality rates from the acute respiratory infections are in general higher in northern than in southern urban areas. This is indicated by Table 4, which embodies data from a few typical southern states and some states of the North having a large negro population. The ratios of deaths from pneumonia to total deaths are based on deaths in urban areas from 1921 to 1929, and the death rates per 100,000 are calculated for 1929, which are fairly typical of those for the other years. The data give reasonable support to the following conclusions as to the relation of mortality rates from pneumonia:

For the rural population death rates from pneumonia in the North exceed those in the South very much more in the colored than in the white population. The data are doubtless influenced by the fact that in the North the proportion of colored inhabitants other than negroes is much greater than in the South, but in the states studied the proportion of other colored is in no case as great as 25%.

In the colored population of the South, urban and rural mortality rates differ much more than in whites.

In the colored population of the North, rural and urban mortality rates from pneumonia differ much less than in the South. Pneumonia rates in southern rural negroes are relatively low.

In the white population of the North death rates from pneumonia are probably enhanced more than in the South on account of the higher proportion of foreign-born inhabitants, among whom mortality from pneumonia is relatively high.

The rural white population, which differs less between North and South than the urban whites or either the urban or rural negroes, shows little change in pneumonia mortality in relation to latitude. I have calculated the pneumonia death rates of the white rural population in several states, both North and South. In 1932, for example, these rates per 100,000 inhabitants were as follows in a few typical states of the South: Alabama, 54; Florida, 39.6; Georgia, 58.5; Louisiana, 48.9; Mississippi, 42.9; North Carolina, 64.7; South Carolina, 64.9; Virginia, 61.5. In a sample of northern states the rates were: Illinois, 66.3; Pennsylvania, 71.2; New York, 77.5; Michigan, 64.9; Ohio, 68.6; Massachusetts, 74; Wisconsin, 64.8. A calculation of the mortality rates for pulmonary tuberculosis in the rural white population in the same states for 1932 gives the following data: Alabama, 39.8; Florida, 38.9; Georgia, 30.2; Louisiana, 26.5; Mississippi, 35.1; North Carolina, 38.7; South Carolina, 26.2; Virginia, 56.8; Illinois, 59.6; Pennsylvania, 54.2; New York, 74.6; Massachusetts, 113.3; Michigan, 47.1; Ohio, 46.8; Wisconsin, 47. Tuberculosis, like pneumonia, is apparently more fatal to the rural white population in the North than in the South. This conclusion is, of course, what one would expect in the light of seasonal fluctuation in mortality from these diseases.

The migration of negroes from the rural South to the cities of the North, where they become crowded together in limited spaces that favor the spread of all sorts of infections to which they have previously built up little resistance, has resulted in many deaths. Not improbably the negro will in time acquire a greater measure of immunity to these infections, as other races have done. In fact, there is evidence that the American negro has developed a partial immunity to tuberculosis which renders him less apt to succumb than are colored races that have not been in frequent contact with this disease. But even if the negro develops a degree of resistance to pulmonary infections comparable to that of the whites, he will probably continue to be handicapped by his inferior status for many years. Whether or not the genetic constitution of the negro predisposes him to fall a victim to respiratory diseases, these diseases will nevertheless continue to constitute selective agents acting on the basis of racial heredity. The skin color and other anthropologic characters that cause negroes to be identified as such and lead to their segregation in unfavorable surroundings or their employment in less remunerative occupations constitute indirect causes of selective mortality. These anthropologic characters may not have the slightest direct connection with death from any cause whatever, but if they have an indirect influence, even through the effects of poverty, ignorance, or race prejudice, they may lead to the selective elimination of their possessors. For these reasons, if for no others, respiratory disease will continue to be more fatal to negroes, so long as the social and economic relations of the races remain essentially as they are at the present time.

Another circumstance that increases the racially destructive effect of respiratory disease among the negroes is their relatively high death rates from these diseases in early adolescent and middle periods of life. From the standpoint of racial survival it matters relatively little what happens to people after they have passed the reproductive period. The age distribution of deaths from both tuberculosis and the acute respiratory infections is much more of a handicap to natural increase in negroes than in whites, and since cities, both North and South, attract negroes in the adolescent and middle age periods, their racially destructive influence is all the more potent.

Summary. Seasonal fluctuations in mortality from tuberculosis and the acute respiratory infections were studied in the white and colored populations of 9 states in which deaths from different diseases were classified by month and by color over a 10-year period from January 1, 1921, to December 31, 1930.

For the pneumonias and bronchitis, the lowest mortality for both races occurred in July or August, and the highest in January or February.

The extent of seasonal fluctuations in mortality was greater from lobar (and undefined) pneumonia than for bronchopneumonia in both the white and colored populations.

The seasonal fluctuations in mortality from influenza were greater than those in mortality from the pneumonias.

Mortality from tuberculosis varies much less with seasons than mortality from the acute respiratory infections.

The highest and lowest mortality from pulmonary tuberculosis occurred about 2 months later than the highest and the lowest mortality from the pneumonias and bronchitis.

The seasonal fluctuations of mortality from lobar pneumonia and bronchopneumonia were significantly less in the colored than in the white population, not only in the whole area studied but also in the several states and in each of 6 large cities, both North and South. For the entire area mortality from influenza and bronchitis, and, to a less extent, from pulmonary tuberculosis, showed a greater seasonal fluctuation in the white than in the colored population.

For all races death rates from respiratory diseases are higher in cities than in rural areas under comparable climatic conditions.

Differences in respiratory death rate between urban and rural areas of the South are very much greater in the colored than in the white population.

Although death rates from pneumonia in the colored population are higher in some large cities of the South than in most large cities of the North, these rates are in general higher in northern than in southern cities.

The mortality from pneumonia and tuberculosis in the colored people of the North is nearly as high in rural as in urban areas. Differences in mortality from respiratory diseases between the rural

South and the urban North are very much greater in the colored than in the white population.

In their effects on mortality from tuberculosis and acute respiratory infections cities are relatively much more destructive to negroes than to whites. Under present conditions mortality from respiratory disease acts as a powerful check to the natural increase of the negro race in northern latitudes.

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ESSENTIAL HYPERTENSION IN THE NEGRO.

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All studies on heart disease in the American negro,[5 6a, 9 12a b 13 16] including negroes residing in Jamaica,[14] stress the predominance of hypertension as an etiologic factor. There is also reported a greater incidence of hypertension in the negro than in the white race. In a group of 1000 negro male factory workers employed in the Cincinnati metropolitan area, 249 had hypertension; whereas of 1000 white male workers in the same community and approximately the same age distribution, only 91 had hypertension.[2] Adams[1] found the blood pressure of apparently healthy negro industrial workers to be higher than that of white employees. The pressures after 40 years of age advanced more rapidly in the colored than in the white race. Alvarez and Stanley[3] found that the blood pressure rises more rapidly with age in negro than in white prisoners.

The present report is a study of the manifestations of essential hypertension in the negro as observed at the Louisville City Hospital.

In consecutive order, there was analyzed the records of 1198 negro patients admitted to the hospital with an elevated blood pressure which was considered to be essential in type. In most instances, the patients were admitted to the wards for some complication of the hypertension. In the remainder, the elevated blood pressure was found in the course of a routine physical examination. Only adults over 20 years old were included, since few children are admitted to this institution. These observations are compared with 989 white patients with essential hypertension admitted to the hospital during the same period.

TABLE 1.—AGE AND SEX INCIDENCE OF ESSENTIAL HYPERTENSION IN NEGRO CONTRASTED WITH WHITE RACE AND CONTROL GROUPS.

Age.	Hypertension.								Control.							
	Negro (1198 cases).				White (989 cases).				Negro (1666 cases).				White (2724 cases).			
	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.	M.	F.	Total.	Total, %.
20-24 . .	..	1	1	0.1	..	3	3	0.3	101	140	241	14 4	157	284	441	16.2
25-29 . .	8	2	10	0.8	.	1	1	0 1	110	140	250	15 0	139	264	403	14.7
30-34 . .	10	23	33	2 8	4	6	10	1.1	92	112	201	12 3	159	133	292	10.7
35-39 . .	28	49	77	6.4	8	13	21	2.1	151	134	285	17 1	144	146	290	10.6
40-44 . .	58	65	123	10.2	15	17	32	3 2	87	78	165	9 9	105	102	207	7 6
45-49 . .	73	97	170	14.2	38	41	79	7 9	104	73	177	10 7	131	56	187	6 8
50-54 . .	107	95	202	16.8	67	42	109	11.1	58	45	103	6.2	125	99	224	8.2
55-59 . .	74	71	145	12.1	60	47	107	10 9	37	20	57	3.4	112	73	185	6.8
60-64 . .	87	55	142	11.8	102	53	155	15 7	36	41	77	4.6	103	35	138	5.1
65-69 . .	81	49	130	10.9	97	60	166	16 6	41	6	47	2.8	105	35	140	5.2
70-74 . .	51	31	82	6.9	92	52	144	14.5	21	10	31	1.8	70	32	102	3.7
75-79 . .	31	15	46	3.9	58	36	94	9.5	11	2	13	0.8	42	15	57	2.1
80-84 . .	12	7	19	1.5	27	16	43	4.4	7	4	11	0.7	27	12	39	1.1
85-89 . .	9	6	15	1.3	9	10	19	1.1	1	1	2	0.1	9	7	16	0.7
90+	..	3	3	0.3	5	1	6	0.6	3	..	3	0.2	...	3	3	0.1
	620	569	1198	100.0	582	407	989	100.0	860	860	1666	100.0	1428	1296	2724	100.0

Age and Sex Incidence. Table 1 shows the age and sex distribution of the cases which occurred in each 5-year period contrasted with the white patients, along with 4390 non-hypertensive individuals (1666 negro and 2724 white), admitted to the hospital for a 6-month period (July through December, 1936). There were 629 men and 569 women. The greatest incidence (16.8%) occurred in the 50 to 54-year age period. A majority of the cases (76.0%) were from 40 to 70 years. In the white race, the maximum number of cases were to be found in the 60-year age group, and 78.3% were from 50 to 80 years of age. Below the fortieth year, there was a much higher incidence than in the white race, 10.1% in contrast with 3.6%. In the control patients, 58.8% of the negroes and 52.2% of the whites were less than 40 years of age. From this it is evident that the greater incidence of hypertension in the negro in the younger age groups was not the result of admission to the hospital of younger negro patients.

An analysis of the sex incidence with reference to age shows that hypertension manifests itself earlier in the female than in the male, there being 41.6% of the female cases before the fiftieth year and only 28% of the male patients. The percentage age frequency curve (Fig. 1) shows that the curve for the women reaches a peak 5 years earlier than the men. The per cent incidence of the total number of each sex in the fourth decade was twice as great in the women as in the men. In the women 57.6% of the cases were from 40 to 60 years of age; in the men 55.5% were in the 50- to 70-year groups. These conclusions apply likewise to the white patients. This earlier incidence of hypertension in the negro female is only slightly influenced by the greater frequency with which young females enter the hospital. Thus 46.6% of 1382 control cases below 50 years of age were men, and 53.4% were women.

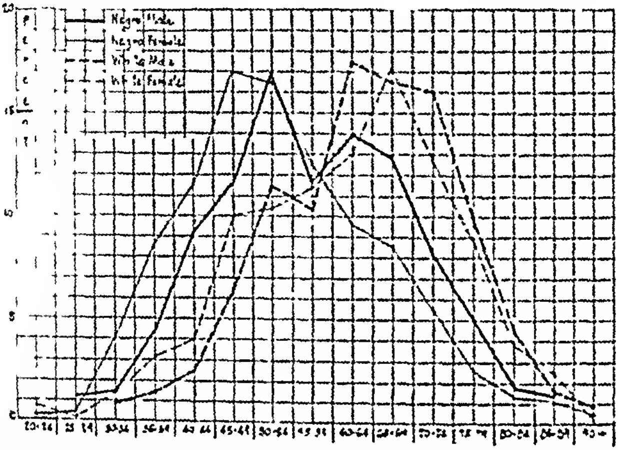

FIG. 1.—Percentage frequency curves in five-year age groups of hypertension in negro and white males and females.

The relative incidence of the sexes was calculated on the theoretical basis that equal numbers of each sex were admitted to the hospital.[10] With this method of determination it is found that there was practically an equal distribution of the two sexes, 50.9% occurring in men and 49.1% in women. On a like basis of calculation the sex distribution in the white patients showed a slight preponderance of women, 56.5% and 43.4% in the female and male cases respectively. These observations are similar to those of Schwab and Schulze[12a,b] in negroes of Texas with hypertensive heart disease except that they found this type of heart disease to occur $1\frac{1}{2}$ times more often in the negro female than in the negro male. Others[9,13] have also reported that hypertensive heart disease reaches its point of greatest frequency a decade earlier in the negro than in the white race.

Major Complications. The major complication, namely cardiac, cerebral (hemorrhage, thrombosis, embolism) and renal were especially analyzed. Only patients with uremia were placed in the renal group. Table 2 is the distribution of these chief clinical types compared with the white patients. One or more of these complications occurred in 75.7% of the cases in contrast to 66.2% in the white patients. They were present in 84.5% of the 629 men and 66.3% of the 569 women. Similarly, more white male patients suffered these complications, 71.5% and 58.5% in the male and female sexes respectively. In both races it was rare to find a patient in uremia without coincident heart failure, or a cerebral vascular accident. The cardiac and cerebral groups were usually distinct types. Of these major complications, myocardial insufficiency accounted for 68.4%, cerebral vascular accidents occurred in 22.0% of the patients, and 9.6% had uremia. There was practically a similar distribution among the white cases. The individual complications occurred with an approximately equal frequency in the sexes of both races. Table 3 is the percentage age frequency with which the cardiac, cerebral and renal cases occurred in each 10-year age period. The point of greatest frequency reaches

TABLE 2.—ANALYSIS OF MAJOR COMPLICATIONS.

	Negro (1198 cases).					White (989 cases).				
	M.	F.	Total.	Total cases, %.	Cases with complications, %.	M.	F.	Total.	Total cases, %.	Cases with complications, %.
Cardiac (uncomplicated)	366	238	604	50.4	. .	261	163	424	42.9	
Cardiac + cerebral . .	10	14	24	2.0		7	7	14	1.4	
Cardiac + uremia . .	40	26	66	5.5	. . .	25	7	32	3.2	
Cardiac + cerebral + uremia	2	. .	2	0.2		. .	1	1	0.1	
CARDIAC . . .	418	278	696	. . .	68.4	293	178	471	. . .	66.0
Cerebral (uncomplicated)	97	86	183	15.2	. . .	110	48	158	16.0	
Cerebral + uremia . .	8	7	15	1.2	. . . .	8	5	13	1.3	
CEREBRAL . .	117	107	224	. .	22.0	125	61	186	. . .	26.0
Uremia (uncomplicated)	8	6	14	1.2		5	7	12	1.3	
UREMIA . . .	58	39	97	. .	9.6	38	20	58	. . .	8.0
Total	531	377	908	75.7	100.0	416	238	654	66.2	100.0

TABLE 3.—PERCENTAGE AGE FREQUENCY OF MAJOR COMPLICATIONS.

	Negro.			White.		
Age.	Cardiac.	Cerebral.	Uremia.	Cardiac.	Cerebral.	Uremia.
20-29	0.7	0.9	. . . .	0.2	. . . .	. . . .
30-39	8.0	4.5	8.2	3.2	2.7	3.5
40-49	24.6	24.1	30.9	9.1	12.8	12.0
50-59 . . .	30.2	33.5	28.9	21.6	20.4	25.9
60-69	23.9	20.5	18.6	35.3	34.9	31.0
70-79	9.8	13.8	12.3	22.7	24.3	19.0
80+	2.8	2.7	1.0	7.8	4.8	8.6

a peak 10 years earlier in the negro than in the white patients. Uremia in both races occurred more frequently in the younger age groups. Bell and Clawson[4] found that the average age in the renal was lower than that in the cardiac and encephalic types of essential hypertension.

Angina Pectoris. A classical history of angina pectoris was obtained in only 6 cases (0.5%). There was a similar low incidence in the white patients, 1.5%. Numerous authors have commented on the infrequency with which angina pectoris is encountered in negroes. In this institution, cardiac pain is rarely found in a negro even with clinical and electrocardiographic evidence of coronary artery sclerosis. Roberts[11] attributes it to the lack of mental stress and strain in the negro. Schwab and Schulze[125] believe it is due to an inherent difference in the sensitivity of the nervous systems in the white and negro. Neither of these explanations is entirely sufficient, since angina pectoris is also infrequent in the white patients admitted to this institution. In articles on angina pectoris there are numerous comments on the comparative infrequency with which it is encountered in patients confined in charitable institutions. Hamman[7] believes this is due to their low level of intelligence. It is of interest that the more unmistakable histories of angina were obtained in the white patients who were above the intellectual and social level of the average patient admitted to the wards of this municipal hospital. The economic depression necessitated their admission to a free institution. Multiple factors are responsible for the low incidence of angina pectoris in the hospitalized negro. 1. Lack of intellectual ability fully to interpret and describe the sensation of cardiac pain; 2. The distress of myocardial, cerebral or renal failure symptoms can obscure all history of angina pectoris; 3. Uncomplicated anginal type of heart failure is usually the complaint of an ambulatory patient.

Auricular Fibrillation. This was present in 83 cases (7.0%). The white patients had a slightly higher incidence (10.6%). Table 4 gives the age and sex incidence. While the youngest case in both races was 42 years of age, there was a greater incidence a decade earlier in the negro than in the white patients. The male sex predominated in both races. Over 80% of the cases of auricular fibrillation were associated with congestive heart failure. Flaxman[66]

TABLE 4.—AGE AND SEX INCIDENCE OF AURICULAR FIBRILLATION.

	Negro.				White.			
Age.	Male.	Female.	Total.	Total, %.	Male.	Female.	Total.	Total, %.
40–49 . .	4	5	9	10.8	1	2	3	2.9
50–59 . .	10	9	19	22.9	12	8	20	19.0
60–69 . .	20	11	31	37.4	24	11	35	33.3
70–79 . .	13	6	19	22.9	26	13	39	37.2
80–89 . .	4	1	5	6.0	4	3	7	6.6
90+ . .	..	..	.	...	1	..	1	1.0
Total .	51	32	83	100.0	68	37	105	100.0

found that 9.8% of colored and 32.3% of white patients with hypertensive heart disease had auricular fibrillation.

Syphilis. The incidence in this hospital of syphilis in the negro with primary hypertension has been reported.[8] Of 369 negroes 112 (30.4%) had a serum reaction positive for syphilis; whereas only 9.5% of 297 whites had serologic evidence of the infection. In a control group, 32.6% of the negroes and 18.8% of the whites had a positive Wassermann.

Diabetes. Diabetes of varying severity was present in 45 patients of each race, 3.7% in the negro and 4.5% in the white. The number of cases of each sex was as follows: negro males, 10; negro females, 35; white males, 15; white females, 30. There was no case in the white race below the age of 40, but there were 3 negro females in the fourth decade. Congestive failure was present in 11 of the negro and 6 of the white diabetics. A cerebral vascular accident occurred in 3 patients of each race. Bell and Clawson[4] state that 5.5% of hypertensive persons over 50 years have diabetes. White[15] found that 1.5% of his cases of hypertensive heart disease had coincident diabetes.

Summary. 1. A study is presented of the manifestations of essential hypertension in 1198 negroes admitted to the Louisville City Hospital, compared with 989 white hypertensives admitted to the wards during the same period.

2. Hypertension occurred a decade earlier in the negro than in the white race. In the negro, 10.1% of the cases were below the fortieth year in contrast with 3.6% in the whites.

3. The percentage age frequency curve reaches a peak 5 years earlier in women than in men. This applies likewise to the white patients.

4. There was an equal distribution of the sexes. The white hypertensives showed a slight preponderance of women.

5. One or more of the major complications of hypertension—cardiac, cerebral and renal—occurred in 75.7% of the cases in contrast to 66.2% in the white patients. In both races, more male than female patients suffered these complications.

6. Myocardial insufficiency accounted for 68.4% of these major complications, cerebral vascular accidents occurred in 22.0% of the patients and 9.6% had uremia. There was practically a similar distribution among the white cases.

7. Individual complications occurred with an approximately equal frequency in the sexes of both races.

8. The percentage age frequency curve of the cardiac, cerebral and renal cases reaches a peak 10 years earlier in the negro than in the white.

9. Angina pectoris was relatively infrequent in both negro and white.

10. Auricular fibrillation had a slightly higher incidence in the white race.

11. The incidence of syphilis was no greater than in non-hypertensives. This applies to both blacks and whites.

12. Diabetes was present in 3.7% and 4.5% of the negro and white cases respectively.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

III. THE LACK OF INFLUENCE OF VITAMIN B (B_1) ON WATER RETENTION IN THE TOXEMIAS OF PREGNANCY.*

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THE physiologic strain of childbearing requires dietary factors to be increased over the standard requirements for women. During pregnancy, various conditions favoring nutritional instability are apt to arise, such as alteration in the gastro-intestinal tract secretions, vomiting and perverted appetite. Thus during pregnancy it is not unusual to see the development of nutritional deficiency disorders such as hypochromic and macrocytic anemia, hypoproteinemia, polyneuritis, and other distinctive vitamin and mineral deficiency syndromes.

Recent studies by Elsom,[2] Weiss and Wilkins[5] and others have indicated that a deficiency of vitamin B_1 may result in water retention irrespective of the level of the plasma proteins and venous pressure.

The importance of water retention and its relation to hypoproteinemia in the true toxemias of pregnancy have been pointed out in the preceding papers of this series.[4a,b] It was shown[4a] that the administration of a diet containing 260 gm. of protein daily

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* This study was aided in part by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

and the parenteral injection daily of 750 Sherman units of vitamin B_1 and 5 cc. of a solution of liver extract which was derived from 25 gm. of liver and was rich in other portions of the vitamin B complex to 10 pregnant women resulted in striking losses of body weight and the disappearance of edema. Each of these women had marked water retention associated with hypoproteinemia. In 6 other pregnant women, however,[4b] the same effects were obtained with the high-protein diet alone. However, since such a diet is in itself relatively rich in the vitamin B complex, it remained possible that the effects secured were the result not of the protein as such but of its vitamin B_1 content.

Methods. In order to decide this point 3 women in the last trimester of pregnancy were selected for study, each of whom presented suggestive evidence of vitamin B deficiency. Each had generalized edema of severe grade, and each had been on a low-protein diet throughout pregnancy. The first 2 patients complained of numbness and tingling of the extremities. These symptoms were consistent with an early stage of polyneuritis, but objective evidence for this was lacking. The third had had persistent vomiting for 6 months. The plasma protein levels of the 3 women were such that the calculated oncotic pressures[6] were 195, 195, and 243 mm. of water, respectively. The venous pressures respectively were 11, 11, and 9 cm. of water.[3] The 3 patients had gained during pregnancy 35, 53, and 23 pounds, respectively. On admission to the hospital, their blood pressures were 136 systolic and 90 diastolic, 184 systolic and 100 diastolic, and 160 systolic and 104 diastolic, respectively. Albuminuria was present in each.

Each patient was ambulatory on the hospital ward. The usual house diets were supplied. No restriction of salts or fluids and no purgation were employed. Commencing on the fourth day, each received by intramuscular injection daily for 4 days 20 mg. of synthetic crystalline vitamin B_1* (at least 8000 Sherman units) and 5 cc. of a solution of liver extract* derived from 25 gm. of liver (fraction G of Cohn, Minot, *et al.*[1] According to Weiss and Wilkins,[5] this amount of vitamin B_1 produces a marked and prompt loss of weight in patients with edema due to vitamin B_1 deficiency.

Results. No significant change in edema or weight occurred in any patient during a period of 1 week beginning with the first day of administration of the vitamin. The arterial blood pressures and the quantitative output of albumin in the urine were likewise unaltered. Symptoms remained unchanged.

As to control for these observations it may be noted that 6 pregnant women with a similar condition given a high-protein diet[4b] showed a weight loss in 1 week's time of 2.9 to 4.1% of their original weight.

Discussion. The data presented offer no evidence for the belief that the water retention of pregnancy toxemias depends on a deficiency of either vitamin B_1 or the other components of the B complex found in liver fraction G of Cohn, Minot, *et al.* It is of course possible that vitamin B_1 may influence the absorption or assimilation of protein foods or the manufacture of plasma protein. Such a possibility is not excluded by these data.

Further evidence that the plasma protein level is the significant factor in determining the degree of water retention in pregnancy may be deduced from certain observations, the details of which have been previously reported.[4b] Briefly, after suitable control periods, 20 women in the last trimester of pregnancy with varying plasma protein levels were given sodium (6.3 gm. calculated as Na) chloride or bicarbonate daily. The degree of water retention, as evidence by the percentage gain in body weight after 3 days, has been plotted against the calculated plasma oncotic pressure in Chart I. It is apparent that within limits of error the degree of water retention is inversely proportional to the calculated plasma oncotic pressure.

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* Kindly supplied by Eli Lilly & Co., Indianapolis.

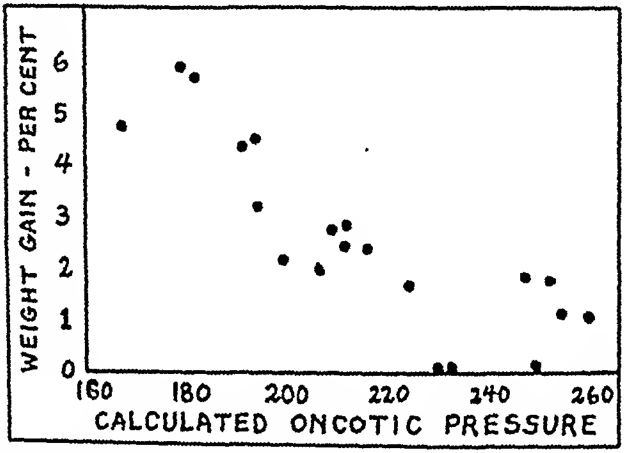

CHART I.—Percentage weight gain in 3 days following the administration of sodium salts to 20 pregnant women plotted against the calculated plasma oncotic pressure in millimeters of water.

Summary and Conclusions. 1. No evidence has been obtained that a deficiency of vitamin B_1 plays a rôle in water retention in pregnancy toxemias.

2. There is an excellent correlation between the level of the colloid osmotic pressure of the plasma proteins and the degree of water retention which may be induced by the administration of sodium salts to pregnant women.

3. Water retention in the toxemias of pregnancy is conditioned chiefly by the level of the plasma proteins.

The writer is indebted to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital for their coöperation which made this study possible. Miss Margaret A. Adams performed the chemical determinations reported in this paper.

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THE BASAL METABOLIC RATE OF CHILDREN WITH SYDENHAM'S CHOREA.

REPORT OF 42 PATIENTS

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SOMETIME ago we observed a young girl who had an irregular tremor, a tachycardia, a soft systolic murmur over the apex of her heart, a moderate pyrexia and a slight loss in weight. It was difficult at the bedside to distinguish between an acute chorea and a mild thyrotoxicosis. The basal metabolic rate was measured in an effort to establish the diagnosis. It was slightly elevated. A review of the standard texts on metabolism and pediatrics[2,5,7,8,10–12,14,16,19] failed to disclose any statement concerning the effect of chorea on basal metabolism.

As it was not unlikely that there had been other cases where the same confusion existed and knowledge of the metabolic rate in chorea would have given additional information of this little understood disease, 42 ambulatory patients were selected from our cardiac follow-up clinic for study. Basal metabolic rates were measured during an acute attack of Sydenham chorea. Twenty had the test quite early in the disease, before the involuntary twitchings were too severe to interfere with the readings. On a number of occasions metabolic estimations were attempted during the height of the disease; but it was impossible to get satisfactory graphs. The 22 others were given basal metabolic tests as soon after the acute phase of the disease had subsided as accurate determinations could be made. In this way, it was believed that any changes in metabolic rate that chorea might induce would be evident either at the beginning or end of the disease.

All readings were made early in the morning during the post-absorptive period. Nearly three-fourths of the group (29) were tested by the Jones metabolometer, the remainder by the Sanborn machine. Calculations were made using the standard tables for children. In those children who ran a slight fever, for each degree of Fahrenheit rise in temperature, 7.3% was deducted. All recorded results have been corrected for pyrexia.

The ages of the children varied from 6 to 14 years; 25 were girls and 17 were boys; 39 were white and 3 were colored. Fifteen had no evidence of cardiac damage, 16 had early mitral stenosis and 11 had a developed mitral stenosis. Of the latter group, 2 followed scarlet fever, 2 had adhesive pericarditis and 2 had free aortic insufficiency in addition to their mitral valve damage.

Basal metabolic rates varied from −24% to +15% with a median at −4.3%. If this average is accepted as the zero point and the conventional 21% range used, the "normal range" for our series would extend from −14% to +6%. This range agrees well with the findings of Jenkins[13] who found the zero point of −7% in a series of 1126 normal men and 2994 women of the same city. Thirty-one children with chorea (74% of our series) had basal metabolic rates that fell within this "normal range." Five readings were above the upper normal limit viz., +15%, +13, +13, +10 and +7% while 5 were below the lower normal limit or −15, −17, −19, −20 and −24%. This spread is in keeping with the ranges observed in many large series,[15-20] as Talbot *et al.*, found practically 95% of all their measurements were between −20.3 and +25.5%.

In 4 patients we were fortunate in measuring the basal metabolic rates both early and late in the disease. E. W. had −15% early in the disease, −15% a year later and again early in another mild attack of chorea, and −20% several months after the latter attack had subsided. The rates of the other three varied from +15, +6, and −4% early in the disease to +10, −8 and −11% after it had subsided. No exact correlation between the rates early in the disease and those taken later could be made, however, it appeared in general that the basal metabolism was slightly lower after the disease began to wane. Neither did the severity of the disease affect the metabolic rate. Patients were arbitrarily classified as mild, moderate and severe on the basis of their muscular activity, fever, and exhaustion. Careful analysis of these groups failed to show any appreciable difference between groups as all classes showed a similar range of metabolic rates (Fig. 1).

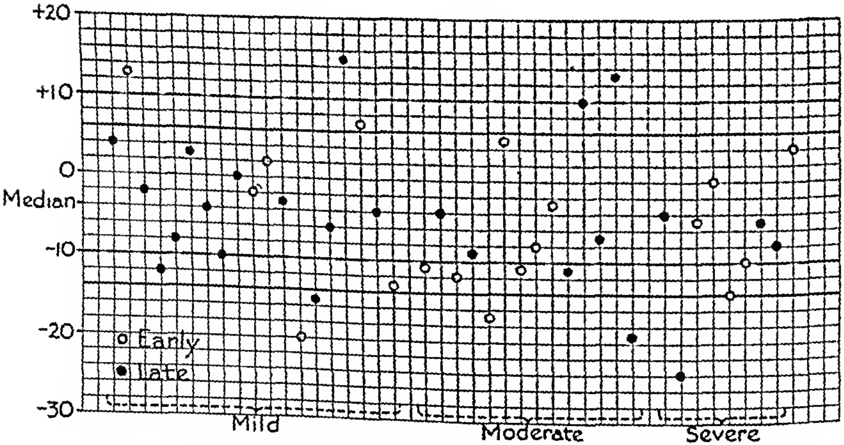

FIG. 1.—Graph showing the distribution of the basal metabolic rates of 42 children with Sydenham's chorea.

Discussion. An extended search of the literature disclosed several references concerning basal metabolism in chorea. Paulian, Padéano and Avicesco[18] (1927) concluded from a study of 3 young girls that chorea greatly reduced the metabolic rate. Two years later Parhon and Ornstein[17] reported the changes of metabolic rate of 7 patients: in 5 it varied from −3 to +8%, and in a sixth it was +24%, while the seventh patient had a chronic Huntington chorea. The subject was more carefully studied by Warner[21] in 1930. He examined 5 children both in the active and recovered phase of chorea, who showed neither pyrexia nor enlargement of the thyroid gland. The rates were within normal range, except one a +32.7% in a severe chorea. Gerstley[9] classified the basal metabolic rates of choreic children in two groups; averaging between +2 and +4% and averaging between +12 and +14%. Unfortunately, he offers no explanation for these two groups.

The muscular twitchings of chorea have been the subject of much speculation. It was formerly believed to have been a peculiar or partial contraction of the muscles. The subject was critically studied by Stanley Cobb.[6] By means of non-polarizable electrodes he transmitted the action currents of the affected muscles to a string galavanometer and recorded them on moving paper, a procedure similar to electrocardiography. Action currents of voluntary muscular contraction showed very little qualitative difference from the twitchings of chorea.

Increase of basal metabolic activity after muscular exercise has been known for a long time. As early as 1898 Rubner and Huebner observed that a restless infant produced more heat than a quiet one. Benedict and Talbot[4] devised a special apparatus which enabled them to record movements of the bed as well as heat production. They found that very small infants who were normally active had 25% more heat production than the normal basal rates gave. Similarly Benedict and Carpenter[3] demonstrated that a normal man used 17% more oxygen when standing than when seated. The seemingly slight muscular activity needed for standing moderately increased the metabolic rate. From this it has been suggested that the tremor of exophthalmic goiter is largely responsible for the increased metabolic demands of that disease. While this may be a factor, it probably is a minor one. Aub, Bright and Uridil[1] studied the effect of thyroxin on the basal metabolism of cats. They found an increase of metabolism following the administration of thyroxin that could not be explained by increased muscular activity, muscular fibrillation or increased muscle tone, and concluded that thyroxin was a direct stimulant of oxidation of the body cells. It is a frequent clinical observation that hyperthyroid patients without any appreciable tremor have an exaggerated basal metabolic rate. Hamburger first called attention to the clinical entity and he has called the condition "masked hyperthyroidism."

From our results it is apparent that chorea, itself, does not greatly alter the basal metabolism. Tests were made both early and late in the disease, and the latter were only slightly lower than the former.

All readings were made before the muscular contractions and twitchings were marked, since it was impossible to get proper readings during the height of the disease. Increased muscular activity undoubtedly raises metabolism, but its study would involve more elaborate apparatus. It is also true that a developed active chorea presents no differential diagnostic problem as it is recognized at sight. However, the early and late phases of chorea when satisfactory basal metabolic rates can be determined by the common types of machines in clinical use are conditions that might simulate mild hyperthyroidism.

Conclusions. 1. The basal metabolic rate was measured in 42 children suffering from acute Sydenham chorea and found to be within normal limits.

2. The severity of the chorea apparently did not affect the metabolic rate.

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CHRONIC CIRCULATORY EFFECTS OF TOBACCO AND NICOTINE.

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FOR a generation or more, there has been accumulating a mass of laboratory and clinical data which has been interpreted as indicating a causal relation between the use of tobacco and organic circulatory disease. A careful analysis of the literature revealed that most of the work was improperly controlled and the reasoning highly uncritical. Confirmation or denial was therefore indicated. In connection with another study, material became available for the present investigation, which we believe definitely refutes the many teachings of the past, especially as to the rôle of nicotine in the production of lesions of the heart and blood-vessels.

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In 1902, Esser[20] described degenerative changes in the vagus nerves of dogs chronically poisoned with nicotine salts. He failed to find degenerative changes in the heart muscle, and concluded that the cardiac irregularities in heavy smokers reported by earlier writers, were due to the degenerative changes in the cardiac nerves. Several papers appeared in the years 1906 to 1908[1,4,7,22,23,40,42a,78] reporting changes in the media of the aorta of rabbits given doses of nicotine, tobacco infusion or solution of tobacco smoke. Some of the experimenters administered the poison by stomach tube, others by intravenous or subcutaneous injections. In most instances; there was no mention of the number of animals employed, and only one experimenter[42a] in this period reported the examination of the blood-vessels of control animals. Lesieur[42a] controlled his experiments by administering infusion of denicotinized tobacco to one group of rabbits and infusion of ordinary tobacco to the other group. None of the rabbits which received the denicotinized tobacco showed vascular degenerative changes. Little weight can be given to this report since "denicotinized" tobaccos contain one-fourth to one-half as much nicotine as untreated tobaccos, a fact not appreciated at the time of Lesieur's experiments. All of these early writers mentioned degenerative changes in the media. Some described aneurysms of the aorta[1,7,22] athermatous plaques[4,7,22] and changes in the intima.[22] Adler and Hensel[1] denied degeneration of the intima, or inflammatory lesions; the pathology of the media they characterized as degenerative or calcareous, similar to that produced by epinephrine. There were, however, no cerebral hemorrhages, in contrast to epinephrine.

Some years passed before general interest was again aroused in the vascular effects of chronic tobacco poisoning. Clinical opinion was divided as to an elevation of blood pressure in chronic smokers. Studies by Brigham,[8] Earp[18] and W. M. Johnson[33] showed no difference in blood pressure between smokers and non-smokers, but W. F. Dixon, the pharmacologist[17] affirmed that chronic smokers exhibit a hypertension, and Knopf[34] accepted the dogma that smoking augments cardiovascular disease. Külbs[35] described 3 cases of hemiplegia which he attributed to tobacco.

Pawinski[51] reported that 42% of cases of coronary disease were in heavy smokers, but that only 23% of generalized arteriosclerosis were from this group. Ralli and Oppenheimer,[54] Cornwall[13] and Moschcowitz[47] accepted the view that some cases of angina pectoris are due to tobacco smoking, and Plenge[53] observed coronary sclerosis, due chiefly to connective tissue replacement of the muscle and elastic fibers of the media, with evidence of fresh necrosis also, in two supposed victims of tobacco smoke. As early as 1915, Brooks[9] attempted an experimental study and saw necrosis of the myocardium, especially of the papillary muscles in rabbits injected with nicotine.

The lesions of thromboangiitis obliterans are well recognized and are known to be statistically related to the use of tobacco (Silbert[61]). Proof of a cause and effect relationship is lacking, although several investigators[25,26,65a,b,69] have shown a high incidence of skin sensitivity to tobacco in this disease. Some constituent other than nicotine was responsible for the skin reactions.

During this period of active clinical interest Romm and Kuschnir[55] renewed the experimental attack. They injected some rabbits with epinephrine, others with nicotine. Epinephrine injected rabbits exhibited sclerotic plaques in great vessels and a decreased response of perfused coronary and renal vessels to constrictor and dilator drugs, earlier and more extensively than the nicotine-injected animals. Control animals were studied but the history and treatment of the controls was not described in the article.

Experiences with intravenous injections of nicotine in rabbits were related by Kosbota[35] in 1930; there were vascular lesions similar to those reported by the earlier writers; calcareous plaques were found in the media and the intima was swollen, with fatty degeneration and desquamation of the endothelium. Female rabbits were affected to a greater degree than were males. There were but 4 control animals, out of a total of 21, and no report of observations on the controls was given.

Gangrene of the toes, preceded by blanching of the skin of the toes in male rats chronically poisoned by tobacco extract has been recently reported. The authors, Friedländer, Silbert and Laskey,[21] observed gangrene in toes of but 1 of 12 rats injected with corresponding doses of pure nicotine. Female rats failed to exhibit gangreneous changes, and no such lesions were noted in control rats. Again, it is not clear what treatment the control rats had received.

Numerous other experimental and clinical contributions could be quoted, but it is sufficient to list these among the references.[3,12,28–30,48,49,52,57,58,66,76]

In view of the almost universal failure of the experimenters to adequately control their observations, whereby the effects of diet, weather, infection, handling, and so forth, could be ruled out, we planned the experiments described below. Both rats and rabbits were used.

Method. 1. *Growing Rats.* Growing rats were started on the experiment between the 10th and 60th day of life. There were 6 litters, each of which was divided equally into control and test animals. Except for 3 control females and 3 nicotine-injected females, all the growing rats were males. There were 34 in all. Injections of nicotine, dissolved in 0.9% saline and neutralized to litmus with dilute hydrochloric acid, were made subcutaneously, twice daily, 6 days per week and once on Sunday. The dilution was at first 1 part nicotine in 10,000 parts of saline. This concentration was increased finally to 1 to 1000 or 1 to 500 as the animals grew larger, so that while the initial dose for very young rats was but 0.05 cc., the final dose was 0.3 cc. to 0.5 cc.. In all cases the morning dose was adjusted to produce mild convulsions. The evening dose was always the same as the morning dose, but as was mentioned in a previous report[72] the symptoms following the second injection of the day were milder than in the morning. *Litter mate controls received twice daily injections of saline*, the volume of fluid corresponding to that administered to the test animals. Each cage contained both control and test rats, in order that all uncontrolled factors might be the same for all rats. The duration of the experiments on the growing rats was from 3 to 6 months.

2. *Adult Rats.* For adult rats, we were unable to obtain litter mates throughout, but half-sisters or closely related rats from a uniform stock of females were available. Because of an interest in certain other possible effects of nicotine only female rats were included in the adult group. Of these, there were 20 rats, equally divided between control and test groups.

3. *Rabbits.* Each of 2 litters of rabbits was divided equally into control and test groups, which were treated in a manner similar to the rats. In the control group were 3 males and 3 females; in the test group, 4 males and 3 females. The first injection was made at the age of 29 days and the last at the age of 115 days, except for 1 control male which was lost by accident on the 20th day of the experiment.

Rats and rabbits were killed with chloroform on the day after the last injection. The thoracic contents, with the aorta down to the iliac bifurcation, the liver and kidneys were taken out *en masse*. The right and left chambers of the heart were exposed and the aorta opened from heart to bifurcation for gross study. The skin was removed from hind limbs, which were preserved in 4% formaldehyde with the other tissues. Pieces of tissue were then cut for paraffine imbedding or for frozen section. The portions of tissue taken for sectioning were the left circumflex coronary artery with adjacent heart muscle, the arch of the aorta, the thoracic aorta, the abdominal aorta at the level of the renal arteries, and the popliteal artery. Blocks were cut out of the kidney and liver, also.

The paraffine blocks were sectioned at three levels and stained with hematoxylin and eosin or with Mallory's elastic tissue stain. Frozen sections of the tissues of the adult rats were stained with Sudan III to demonstrate any fatty degeneration which may have occurred.

All the above experiments and procedures were carried out in the Department of Pharmacology and the tissue sections were examined by both authors.

Results. Two control rabbits, 2 nicotine-injected rabbits and 1 control rat exhibited Mönckeberg's type of sclerosis of the media of the aorta; 1 control rat suffered from slight degeneration of the media of the popliteal artery and 1 control rabbit developed slight thickening of the coronary artery. No other lesion of the circulatory system was noted. However, during the course of another experiment, some observations were made which have an important bearing on the interpretation of the results of Friedländer, Silbert and Laskey.[21] They were as follows:

Chronic Nicotinism in Paired Rats. Of 25 pairs of adult rats, a test pair was separated from a control pair by a hardware cloth partition in each of 25 cages. Treatment was in all regards the same as in previous experiments. In view of the report of Friedländer, Silbert and Laskey, the feet of these rats were carefully watched for the development of gangrenous degeneration. Contrary to the findings of these authors, we found such degeneration occasionally in both male and female animals, and in both control and test animals. *Furthermore, in a large cage of 12 stock male rats, closely related to the experimental rats, 8 animals developed marked gangrene of the toes.*

Comment. The fact that clear cut degenerative changes occurred in our control groups as well as in the test animals, indicates how little weight can be given to the uncontrolled experiments of the early part of this century. This is especially so since the number of animals in these early investigations was either very small (only 2 in Lee's study) or not given. One cannot so easily dismiss the experimental findings of Romm and Kuschnir[65] and of Friedländer, Silbert and Laskey.[21] It is clear that their observations were better controlled than those of earlier experimenters; but in view of the appearance of gross lesions of the toes of our control rats, their conclusions must be viewed with considerable doubt. Such observations as those of Plenge[63] on human cases must be viewed with skepticism because of the lack of adequate control.

The recent inquiries into the rôle of sensitivity to tobacco in vascular disease requires serious consideration. Harkavy[25,26] and Sulzberger[68a, b, 69, 70] independently examined patients with angina pectoris or thromboangiitis obliterans for skin sensitivity to tobacco and to nicotine. Whereas 76% of such cases exhibited positive patch tests with tobacco, only 36% of smokers with Buerger's disease and 16% of non-smokers gave positive reactions. Nicotine was shown not to be the ingredient responsible for the positive skin responses. Neither Harkavy nor Sulzberger believed they had proven a relationship between tobacco and vascular disease, but considered their data to be suggestive. In this we concur.

The early writers believed that the lesions they saw in experimental animals were due to the repeated vasoconstriction following daily administrations of nicotine or tobacco. Tests of human blood pressure effects during and following smoking have not given uniform results. Most of Lee's subjects[40] suffered a blood pressure rise, which was less in "tolerant" smokers than in novices. Coller[14] found a rise of blood pressure when his subjects smoked tobacco, but fake smoking produced no pressor effect. Aikmann[2] and Thompson and Sheldon[73] reported that as many, or more, subjects exhibited a fall of blood pressure as responded to smoking with increased vascular tension.

Very little attention has been given to the possible deleterious effects of acute tobacco vasoconstriction in the presence of actual vascular lesions of other etiology. That there is vasoconstriction during and for an hour after smoking has been accepted for a long time and that the vasoconstriction is due to nicotine was demonstrated by Lesieur.[42b] Hoskins and Ranson[31] pointed out that the vasoconstrictor effects of nicotine are due to a central as well as sympathetic ganglion stimulation. Stimulation of the adrenal medulla, with increased secretion of epinephrine, has been added as a hypertensive factor in animals.[11,15] Stewart and Rogoff[65] could demonstrate no effect of nicotine on epinephrine secretion, and criticized Cannon, Aub and Binger[11] and others for using uncritical methods. More recent experiments[19,37,41,56,60,67,71] however, lend strong support to the probable stimulation of the adrenal medulla by nicotine.

That smoking actually produces vasoconstriction and slowing of capillary circulation of the extremities in the human has been amply demonstrated by studies of organ volume[10,62] skin temperature [32,44,45,77] and blood flow[38] before, during and after smoking. The vessels of the forehead and abdomen were not affected. Assuming an existing vascular disorder, such as thromboangiitis obliterans or diabetic sclerosis (Blotner[5]) with the tissues on the verge of gangrene, it is logical to suppose that a vasoconstriction due to tobacco may further decrease the nutrition of the tissue to the point where gangrene would result.

Experiments on the coronary vessels do not so readily support a relationship between angina pectoris and tobacco. Reports from two separate laboratories in 1933 described increased coronary flow. Laubry, Deglaude and Walser[39] measured the coronary flow in isolated rabbit heart, and found an increased coronary circulation with infusion of tobacco and with nicotine in all but excessive doses. Mansfeld and Hecht[46] introduced tobacco smoke into the lungs of the heart-lung preparation of dogs and found only coronary dilatation and increased cardiac output. Bond and Hirschfelder had a similar experience many years before. Although the irregularities of cardiac rhythm occurring in certain patients addicted to heavy smoking have been reproduced in animals,[20,64] these irregularities scarcely contribute to an explanation of angina pectoris. A possibility which occurs to the writers is that there is sufficient increase in epinephrine output to accentuate the symptoms of this malady. That epinephrine does precipitate an anginal attack is accepted by clinicians[14] but that smoking increases the epinephrine output in man is only indirectly suggested by none-too-well confirmed reports of increased blood sugar following smoking.[6,16,24,43] Animal experiments usually show an increase of blood sugar[27,41,50,63] and some of them indirectly indicate an adrenal factor[41] but the doses used were larger than would be obtained through smoking of tobacco. Boldyreff[6] attributed the hyperglycemia to some other factor than nicotine.

White[75] observed transient electrocardiographic changes resembling those of coronary obstruction in a man who exhibited anginoid attacks on smoking, but he considered the change purely functional. Perhaps the clinical measurements of respiratory function by Turley and Harrison[74] and of circulatory response to work[49] with figures slightly, but perhaps insignificantly, in favor of abstainers from tobacco, have some bearing on the subject. However, we must not overlook conclusions of Sharber and White[59] from clinical data that there is no statistical relationship between tobacco and angina pectoris, in view of the fact that there was as high an incidence of angina among non-smokers as among smokers.

Since we have no data relating to the subject, we do not care at this time to discuss "tobacco amblyopia," which recent clinical experience suggests is due to constriction of the vessels supplying the retina.

Summary. 1. Experimental and clinical studies supporting the thesis that chronic tobacco or nicotine poisoning leads to degeneration of circulatory organs, are poorly controlled and therefore of doubtful value.

2. Experiments of the present authors show greater vascular degeneration in control animals than in animals chronically poisoned with nicotine.

3. It is suggested that acute peripheral vasoconstriction associated with smoking may exaggerate the effect of existing vascular disease upon the nutrition of the extremities.

4. Smoking probably does not produce organic disease of the heart.

Since the proof was returned to the editor's office, two papers have come to our attention. Harkavy (*Proc. Soc. Exp. Biol. and Med.*, 36, 381, 1937) reported confirmation of the results of Friedländer, Silbert and Laskey with "nicotine-free" extracts of tobacco, and furthermore showed sensitization of segments of intestine of injected rats to the extract. This important contribution further removes nicotine from its alleged rôle as an etiologic agent in vascular degeneration, and emphasizes the insecure ground of prescribing "nicotine-free" tobacco for patients suffering from Buerger's Disease.

Staemmler (*Virch. Arch. f. Path. Anat.*, 295, 366, 1935) found no vascular lesions in rats chronically poisoned with nicotine, although adrenals and testes were markedly affected.

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THE LUCID INTERVAL AND ACUTE APPENDICITIS.

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A review of the results of the management of patients suffering with acute appendicitis complicated by spreading peritonitis on our services in 3 hospitals, over a period of 4 years, shows that in every instance where death occurred the surgeon did not diagnose the condition pre-operatively. The most frequent error made by both ward and attending surgeon was the failure to recognize the early perforative appendix with beginning spreading peritonitis; in 85% of instances a diagnosis of acute appendicitis only was made. The second most frequent error was their inability to diagnose the gangrenous appendix in the pre-perforative state.

In this discussion the latter group only will be considered. Examination of the clinical records showed that invariably the patient gave a typical history of appendiceal colic before admission, the attending physician elicited localized tenderness in the right lower quadrant and diagnosed appendicitis. Directly before admission, however, all symptoms and signs had disappeared, except a moderate or slight elevation of temperature. Increased tension, rigidity, free fluid and distention were absent. There was, however, diminution of peristalsis. Without exception, the lesion responsible for this "lucid interval" was partial or complete gangrene of the appendix.

In surgery, the word "lucid" has been used to describe a period of mental clearness which occurs between an initial semiconscious or unconscious state and coma in patients who have experienced cranial trauma; this is most frequently observed in rupture of one of the branches of the middle meningeal artery with a resultant extradural hemorrhage. During the lucid interval, the patient may converse normally and present no signs of intracranial change. The duration of this period is dependent upon the rapidity with which the blood escapes from the ruptured blood-vessel and the reaction of the compensatory mechanism to the increased intracranial pressure.

The "lucid interval" as we use it in connection with gangrenous appendicitis is the symptom sign-free period preceding perforation and is dependent upon factors which influence intra-appendiceal pressure. The subsidence of pain, remission of temperature, the absence of tenderness, increased tension or rigidity are due in part to a reduction of intra-appendiceal pressure. The symptoms and signs accompanying an acutely inflamed appendix prior to the development of gangrene are associated with and partially dependent upon increased intra-appendiceal pressure.

At the onset there is usually an obstruction of the lumen of the appendix, due either to a fecolith or a mucopurulent plug. Venous congestion followed by the mobilization of neutrophils, with a consequent swelling of the mucosa and submucosa, local necrosis and formation of gas and pus, all tend to increase intra-appendiceal pressure; the absorption of these products of inflammation tends to diminish it; this varying pressure in all probability accounts for the intermittent pain in the early stages of the disease. During this active period the serosa of the appendix withstands tremendous pressure, because of which death of the tissues beneath is hastened. However, when the pressure becomes so great that the cells of the serosa itself become devitalized, it expands. In gangrenous unruptured appendices we have observed on careful inspection a separation of the serosa from the tissues beneath. Frequently pus can be seen in yellowish streaks beneath the intact peritoneal coat, on the surface of the devitalized muscularis. Following the death of the serosa, the "lucid interval" is fully established.

Pain is absent because the nerve terminals have become devitalized. Without careful study, this lucid period of gangrene cannot be differentiated from the period accompanying recovery. The reason for this is apparent: inflamed tissues are overdistended tissues and a return toward normal is associated with a diminution in size and a reduction in pressure brought about mainly through absorption by way of the lymph or blood streams. A small amount of gas or infectious material may escape from the lumen of the distal portion into that of the proximal portion of the inflamed appendix or into the cecum. This slight reduction in pressure lessens venous congestion, the capillary circulation improves, absorption of the products of bacterial activity by the lymph and blood streams is increased and resolution follows.

The frequency with which the symptoms and signs associated with gangrenous lesions of the appendix resemble those of resolution is dependent, 1, upon the management of the patient; 2, the extent of gangrene; and 3, the situation of the appendix. Frequently a physician makes a diagnosis of acute appendicitis, withholds laxatives and fluids by mouth and sends the patient into the hospital. The lucid interval, however, may occur during the time that lapses between the diagnosis and admission to the hospital and accounts for the frequent statement of the patient to the hospital intern that "it is just like going to the dentist with an aching tooth—the pain has gone."

If the surgeon accepts the diagnosis and operates immediately, regardless of the absence of symptoms and signs, a catastrophe may be prevented. If he questions the diagnosis and fluids are withheld until the gangrenous appendix is quarantined, then nourishment given gradually, an appendiceal abscess usually forms. Under such management the symptoms are generally of mild degree and tenderness may be the only physical sign. Peristaltic sounds are usually absent in the right lower quadrant but present in moderate degree throughout the other quadrants. If, however, he does not accept the diagnosis and allows the patient to take nourishment by mouth, the perforation which follows may be sudden and terrific in its effect. Violent abdominal pain at the site of perforation will occur, accompanied by nausea, vomiting and rise in temperature associated with general abdominal rigidity, absence of peristalsis and the presence of free fluid.

The normal appendix has peristaltic waves, but there is no method that we have discovered to determine their presence clinically: neither can we show the effect that inflammation has on the contraction of the muscular coats. In the dog, peristaltic waves occur in the normal appendix and laxatives stimulate them; we do not know definitely what happens after the onset of acute inflammation. We were unable to produce peristalsis or perforation of a completely gangrenous appendix by inducing violent peristalsis of both ileum and cecum with the use of laxatives. At least, it did not occur under direct observation, despite the use of Epsom salts, castor oil and hypodermic injections of eserine. The last produced violent peristalsis in both large and small intestines within 4 minutes of the injection.

While the management of the patient before he is admitted to the hospital is the greatest factor in influencing the frequency with which the lucid interval is confused with a regressing inflammation of the appendix, the extent of the involvement of the appendix in the gangrenous process is also very important. Complete gangrene involving all of the coats resulting in a uniformly black appendix is not commonly observed at operation. The usual type is one in which the mucous and muscularis are only partially involved. The size, number and position of fecal concretions in the lumen of the appendix influence the degree of devitalization. There are cases, however, in which embolic factors play a very important part: according to some investigators this occurs most frequently in the later decades of life. It has been our experience that the greater the amount of tissue involved in the gangrenous process, the more complete the period of lucidity.

An abnormally situated appendix makes the differentiation between resolution and early gangrene even more difficult, particularly if the appendix has been previously inflamed. The initial general colicky pain may not even occur, the attack starting with localized pain. Because of the development of a local tissue immunity, the temperature reaction may be slight or normal and abdominal tenderness absent if the appendix is retrocecal or low in the pelvis. Regardless of the location, however, perforation of a gangrenous appendix into the general peritoneal cavity is delayed not only by changes which occur beneath the serous coat but in the peritoneal cavity as a whole and in the tissues contiguous to the diseased organ. These changes are brought about by the absorption of toxin acting on the hematopoietic system and on the plexuses of nerves, within the abdomen: the mobilization of the neutrophils followed by the larger phagocytes (clasmatocytes), is an example of the former; and the hyperemia of the peritoneum followed by a general outpouring of serous exudate, a local formation of fibrin and a diminution of peristalsis is an example of the latter.

The toxins that are absorbed through a gangrenous appendix are easily taken care of by this defensive mechanism, as evidenced by the absolutely safe procedure of closing the peritoneal cavity without drainage, following the removal of a non-perforated gangrenous appendix. When the serous coat is broken, additional defensive measures are necessary. Antibodies are formed to combat toxins in the blood stream. The large central organs, chiefly the spleen and liver, are called into action. Prognosis is dependent, to a great extent, not on what Nature does, but rather on how the patient is managed. The decisions of those in charge influence the outcome.

If the natural body defense is supported by a management which does not interfere with the protective measures already instituted, local tissue as well as general immunity develops and the patient recovers. If the development of one or the other or both is interfered with, the patient will frequently succumb.

The gross changes which occur in the development of a local tissue immunity are characteristic. In man, if the process is limited to the appendix, hyperemia is followed by a decrease in the vascularity of the peritoneum which appears gray and edematous and is frequently covered with a protective layer of fibrin. The omentum, which is often adherent to the appendix or cecum, is thicker, edematous and the venules appear to be dilated. This phenomenon is the result of the reaction of the circulatory, lymph and autonomic nervous system to bacterial antigens. It is similar to the reaction which occurs in a surface cellulitis, except that in the early stages of peritonitis a uniform erythema is observed, while redness in radiating lines usually definitely marks the lymphatic vessels in a spreading cellulitis.

The diagnosis of the pre-perforative stage—the lucid interval—of acute appendicitis is dependent upon the following: 1, A complete history; 2, a thorough physical examination; 3, noting on the patient's clinical record the physical findings of the physician who first examined him; 4, a careful differential count, with observation on the ratio of mature and immature neutrophils and also the relative number of degenerated immature forms.

1. *A Complete History:* Three important points are frequently missing in the clinical record of the patient operated upon for acute appendicitis in the average hospital: 1, The exact time the pain began; 2, whether or not a laxative was administered, the time of administration, the character, kind and size of the dose or doses; and 3, when and how much opiate or sedative was given before admission. Colicky abdominal pain, general at first, the exacerbations centering around the umbilicus, and later localizing in the right lower quadrant, is still the most reliable symptom of an acute inflammation of the appendix.

Other acute lesions of the abdomen requiring immediate surgery, with the possible exception of acute intestinal obstruction, are not accompanied by pain of this character and the lucid interval does not usually occur. In the early stages of acute intestinal obstruction the absence of temperature and leukocytosis, increase in peristalsis, varying degrees of tenderness and a change in the character of the vomitus usually make the diagnosis certain. A lucid interval, however, may accompany acute intestinal obstruction. The early pain associated with this condition is frequently colicky but may subside when the intestine becomes gangrenous. This lucid interval may be prolonged by withholding fluids by mouth or by the use of the Levin or duodenal tube, the decompression produced by the latter accounting for the improvement in symptoms and signs and perhaps delay in operation. The continuity of the devitalized intestine may last as long as 7 days and when perforation does occur, the pain is not so severe and the physical signs are not so marked as in the usual perforation of an abdominal viscus.

In gangrenous appendicitis the percentage of perforations with the development of a spreading peritonitis increases with the dose and varies with the time of administration of laxatives. Frank perforation with accentuation of pain which is continuous and definitely located by the patient occurs more frequently with than without laxatives and still more frequently with multiple than with single laxatives. The lucid interval is more likely to be overlooked when laxatives have not been given or have been vomited immediately after administration. The likelihood of the latter occurring is less in appendicitis than with acute lesions of viscera in the upper abdomen. Following an acute perforation of the duodenum the patient will invariably vomit the laxative or anodyne, given by mouth, immediately; provided, of course, it is given soon after the onset of pain. Vomiting occurs when the autonomic nervous system attempts to prevent leakage into the peritoneal cavity. In intestinal obstruction the relation of vomiting to laxative administration is dependent upon the site of the obstruction.

There are physicians who persist in giving morphine to patients suffering with acute abdominal pain before making their diagnosis. The resident's problem of determining the character and amount of opiate given to the patient before admission to the hospital is simplified if the attending physician witnesses the operation; if he does not and the patient states that he has received a hypodermic or has obtained relief after taking a pill or medicine, an effort should be made to contact the family physician before operation; this may seem an unnecessary procedure but it is definitely indicated if the patient does not have pain and physical signs are indefinite.

Elevation of temperature is of questionable value as a diagnostic aid because it may be absent in the presence of marked lesions and its remission may mean either gangrene or resolution. In 1927, Bower and Clark[1] reviewed the clinical histories of 750 patients who were operated upon for acute appendicitis and correlated symptoms and signs with the pathologic findings. In 279 patients, there was less than 1° rise in temperature on admission.

2. *A Thorough Physical Examination.* Tenderness is the most important physical sign in acute appendicitis. Its significance, I am sure, is not sufficiently appreciated by the average physician. Tenderness alone in the lower right abdomen, without pain, without nausea or vomiting, fever or leukocytosis, is sufficient at times to make a diagnosis of acute appendicitis.

The technique of the examination for this valuable sign is important. The bed should be so situated that the examiner can walk around it. The patient should be lying in the supine position, no pillow supporting his head, entirely uncovered except for a towel over the pubes. He is told to assume a position which is most comfortable and notation is made if there is any difference in the position of the lower extremities; if the right thigh is slightly flexed, the patient is asked to extend it and is then questioned regarding the relative degree of comfort in each position. A small pillow is then placed beneath the head and neck to relieve the strain on the accessory muscles of respiration. The arms should be placed at the sides.

Standing at the patient's left side, the examiner places his left hand on the abdomen; if the weather is cold the hand should be immersed in warm water before palpation is begun. It is important that the hand be carefully applied to the abdomen; first, the entire hand should be gently laid on the upper left abdomen, not on the right lower quadrant. It should remain there until the examiner feels that he has the patient's confidence. This can only be determined by experience, but a return of normal respiratory rhythm and the patient's permitting the abdominal wall to remain in contact with the hand is evidence that one can proceed. The fingers are then alternately flexed and extended as the hand is moved horizontally along the costal margin; in the same fashion the lower left abdomen is palpated. Following this the upper right abdomen is examined, just as gently and deliberately and finally the right lower quadrant.

From the time the hand is placed on the upper left abdomen until the examination of the right lower quadrant is finished, nothing should be said to the patient. The examiner, however, watches the facial expression, noting any change that may occur. In all quadrants the touch should be light, sufficient only to press the muscles and the parietal peritoneum lightly against the abdominal contents. Following the removal of his hand, the examiner asks the patient to designate the most tender area. If he states that tenderness is absent or that there is no difference in the degree at any point, the knees should then be flexed on the abdomen by placing a pillow beneath the thighs and the hand is applied again to the upper left quadrant and the examination repeated.

Again the patient is asked where the pressure annoys him most and if he indicates the right abdomen an attempt should be made to localize the tenderness more definitely by proceeding this time from the upper right abdomen. If the tenderness is more marked in the lower right quadrant, the procedure advocated by Murphy (tenderness elicited by percussion) is carried out. I have advocated this method ever since I first saw this remarkable teacher demonstrate it at one of his clinics. The second finger of the left hand is flexed to a right angle at the mid-carpal joint, the tip placed on the abdomen and the joint struck with the second finger of the right hand. The blow struck by the percussing finger at first must be light—just enough to determine the maximum point of tenderness. It is hardly necessary to mention that the finger tips alone are most sensitive to changes in muscular tension and that palpation of the abdomen should precede percussion tenderness.

I have found the latter valuable in helping to determine the site for the incision in those cases in which the appendix is in contact with the parietal peritoneum. In eliciting tenderness in a patient whose appendix is abnormally situated, the right and left lateral prone positions are sometimes helpful; having the thighs more acutely flexed than in the supine position reduces the degree of tension and organs deeply situated can be more definitely located. Undoubtedly rectal examination is by far the most important aid in differentiating lower from upper abdominal lesions and in helping definitely to diagnose organic disease in a patient who has a hypersensitive nervous system. Contractions of abdominal muscles due to voluntary spasm can be ruled out by this examination. In women, a vaginal examination should be made if possible.

3. *Noting on the Patient's Clinical Record the Physical Findings of the Physician Who First Examined Him.* The physician who first examines a patient with acute abdominal pain has the best opportunity to make a correct diagnosis. This is true, not only during the early but also the successive phases of inflammatory processes involving any of the abdominal viscera, up to the time the terminal stages of a spreading peritonitis develop, when it becomes difficult definitely to determine the organ primarily affected. Fortunately, advanced spreading peritonitis is seldom observed by a physician at his initial visit. The usual history is that more than one visit has been made by the attending physician before the patient is admitted to the hospital.

In the average case this is as it should be. A correct diagnosis cannot always be made at the first examination, but if appendicitis is suspected, and in the presence of acute abdominal pain it must be, the second visit should not be delayed 24 hours: it should not be delayed more than 4. If the physician has made notations of his initial examination, he will observe changes, if not at the end of 4 hours, then surely at the end of 8, which will indicate definitely whether or not the case is an operative one. Unfortunately, the average physician does not make careful notes, which means that the very slight changes significant of advancing or regressing lesions are overlooked.

If then, at the end of 8 hours he is still uncertain, he should ask himself this question: "Is there anything I can do that will help me determine exactly what is wrong with this patient?" What would the physician do if his patient were in a hospital? He would call a surgeon and have a leukocyte count and Schilling hemogram made immediately. All of these things can be done in the home as well as in the hospital. This is not a plea for more consultation work for the surgeon but a procedure suggested to prevent procrastination, to make possible a closer correlation of history, physical findings and gross findings at operation and to avoid the necessity of explaining why patients are sometimes held at the hospital before they are operated upon.

In defense of the family physician it must be admitted that in many instances, either because of the influence of relatives or friends, patients refuse to accept his advice. To protect himself and emphasize the seriousness of the situation a consultation with a surgeon should be advised and, if the patient refuses, the physician should dismiss himself. Every physician no doubt has had the experience of permitting the wishes of a patient to interfere with what he thinks should be done.

If we could always pre-determine the course disease will take; if in acute appendicitis one could definitely state the number, kind and virulence of the microörganisms at work; if the susceptibility of the patient to these microörganisms were known, one could vary the management accordingly. This being impossible, we must manage the mild, average and severe types in the same manner at the onset. If patients object to operation, they should be told that if the appendix is removed when it is intact, they take only 1 chance in 275 of not withstanding the disease; but if they wait until it ruptures, they take 1 chance in 8, increasing the risk 35 times. These figures are only approximate, but they indicate to patients with ordinary intelligence the risk they assume if they delay.

The surgeon may feel that the onus of the high mortality rate of acute appendicitis is for the most part due to things that happen to the patient before he enters the hospital. The family physician may, and in some instances rightly, criticize various methods of hospital management; but the fact remains that both are at fault in one particular, and that is careful notes pertaining to the physical examination of the patient are not made by either. The surgeon himself seldom writes his findings on the clinical record and no effort whatever is made to obtain those of the family physician. In the average case these notations are not important, especially if the appendix is not ruptured, but in this discussion we are dealing with the unusual case: the one patient in 25. This patient is admitted to the surgical ward as the usual case of acute appendicitis. The resident obtains a history which is typical, but the physical examination discloses no definite information. The chief of the service is duly called. He may see the patient, but more frequently he sends his associate, who in turn is uncertain of the diagnosis. It is at this point that the family physician should be consulted and his physical findings noted on the chart. These findings must be considered if an accurate diagnosis is to be made.

Most patients will consent to operation, but there are a few who doubt its necessity and are anxious to avoid it. These reluctant patients will usually give an accurate history but will not admit that abdominal tenderness is present on palpation. It is wise to talk to the family physician in such cases or, still better, to have him come to the hospital. He and the surgeon both will profit by such a conference. If the physician cannot come, perhaps a member of the family who was present when the examination was made can supply the necessary information. We have been very successful in having the family physician present at operation. Some patients, however, are admitted direct from the dispensary without having previously consulted a physician. In such cases, the notes of the physician in the receiving ward are available.

4. *Careful Differential Count With Observation on the Ratio of Mature and Immature Neutrophils and Also the Relative Number of Degenerated Immature Forms.* A neutrophil leukocytosis in a patient suspected of having an acute appendicitis is of diagnostic value in at least 80% of cases. A Schilling hemogram, if made by a competent clinical pathologist, is of additional value. The report of a resident physician, recently assigned to laboratory duty, on the ratio of mature and immature neutrophils and the relative number of degenerated immature forms cannot be relied upon. The greatest value of the Schilling lies in a comparative study of repeated hemograms made by a clinical pathologist who is intimately acquainted with the clinical aspect of the case. Just as the surgeon visits the Roentgen ray laboratory and confers with the radiologist regarding his deductions on the lesion present in a given case, so should he confer with clinical pathologists in cases of doubtful diagnosis of inflammatory origin.

Conclusions. The high mortality of spreading peritonitis complicating acute perforative appendicitis (27 to 40% in the United States) is in part due to the failure of physicians and surgeons accurately to diagnose the acute lesions of the appendix in both preperforative and early postperforative states.

Partial or complete gangrene of the appendix is frequently associated with a subsidence of symptoms and absence of physical signs—the so-called "lucid interval." This is confused with the resolution following an acute involvement of the appendix of less virulent character. The subsidence of symptoms and signs accompanying both is due to diminished intra-appendiceal pressure: the relaxation incident to devitalization of the serosa in the first instance, the absorption of the products of inflammation in the latter. In this communication we have endeavored to emphasize pertinent points which may aid in the recognition of this "lucid interval."

REFERENCE.

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BOOK REVIEWS AND NOTICES.

PHENOMENON OF LOCAL TISSUE REACTIVITY AND ITS IMMUNOLOGICAL, PATHOLOGICAL AND CLINICAL SIGNIFICANCE. By GREGORY SHWARTZMAN, M.D., Bacteriologist, Mount Sinai Hospital, New York. Foreword by JULES BORDET, M.D., Paris. Pp. 461; 47 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1937. Price, $7.50.

IN 1927 the author observed for the first time a peculiar reaction in the skin of rabbits. When he injected a filtrate of typhoid bacilli intradermally only minimal inflammation followed. But if 24 hours later he gave a second injection, this time intravenously, a violent inflammatory reaction occurred at the site of the skin injection, with hemorrhage and necrosis. This is the famed Shwartzman phenomenon. In some way that is even yet not understood, the skin injection alters the tissue locally in such a way that it reacts to an irritant in the blood stream. Certain other bacteria may be substituted for the typhoid bacilli. Moreover, the reaction is not a specific one, for the cutaneous injection may be made with the filtrate of one organism, the intravenous injection with the filtrate of another.

The present monograph summarizes the work of the author and that of many others who have worked on the phenomenon, up to the beginning of 1936. Among the subjects discussed are the nature of the substance that prepares the skin for the reaction—the subject is antigenic and is of the nature of bacterial soluble toxin; the regression brought about in mouse tumors by intravenous injection of the bacterial filtrate; the distinction between the Shwartzman phenomenon and anaphylaxis as well as the Arthus phenomenon; the probable relation of the phenomenon to human hemorrhagic diatheses and hemorrhagic infections; and the therapeutic effect of serums prepared against bacterial filtrates, in the treatment of human typhoid fever, meningococcic meningitis and ulcerative colitis.

The photomicrographs are numerous and excellent. M. McC.

RECENT ADVANCES IN INDUSTRIAL HYGIENE AND MEDICINE. By T. M. LING, M.A., B.M. (OXON.), M.R.C.P. (LOND.), Senior Medical Officer, Bristol Police, etc. Foreword by J. A. NIXON, C.M.G., M.D., F.R.C.P., Emeritus Professor of Medicine, University of Bristol, etc. Pp. 212; 29 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $3.50.

IN this book the author has endeavored to bring together a number of the modern advances which have been made in industrial hygiene, though of 167 citations over half are from before 1930. On the whole, the work is well done considering the small size of the volume, though one regrets the omission of various subjects of live interest. Little if any space is given to biologic agents as industrial hazards, such as those causing tuberculosis, syphilis, anthrax and epidermophytoses. Too little space is given to metallic poisons (lead only being discussed) and to volatile solvents (benzol and its homologues and trichlorethylene only being considered). No space at all is given to changes of atmospheric pressure, such as those causing compressed air illness.

The bibliography following each chapter is quite helpful, though it is to be regretted that there are not more references to American work. Very few German references are cited, and only one or two French, though much good work has been done on the Continent. Unfortunately 43 citations are given for which no references appear.

Considering in more detail the subject discussed, the chapter on Medical Supervision gives an excellent presentation of the duties of the industrial physician. Industrial accidents and their significance and neuroses and industrial fatigue are well presented in considerable detail. There is also a good, well-organized discussion of industrial lighting.

The chapter on ventilation is somewhat disappointing, but contains some good material. The discussion of local exhaust ventilation is inadequate and the importance of proper hood design is not emphasized. Air conditioning as understood in the United States is not clearly described.

The chapters on dust is well written and comprehensive considering the space allowable. A decrease in silicosis in England, due to the preventive measures taken, is noted. It is wisely emphasized that respirators should *not* be relied upon wholly to protect workers from excessive dustiness, but rather some influence external to the workman.

The chapter on noise is excellent and well worth reading. Noise is cleverly defined as sound at the wrong time in the wrong place.

Lead poisoning, which still heads the list of notifiable diseases in England, is very well handled. Periodic basophilic red cell counts are stated to be an excellent check on workers and on working conditions, but the author fails to refer to McCord's work thereon. There is one grave error in the discussion of the treatment of severe lead colic. Aub is quoted as advising the hypodermic use of ammonium chloride (15 cc. of a 5% solution), whereas he actually advised the use of calcium chloride, which would have an opposite effect.

The consideration of industrial gases is rather meager. Henderson and Hagard's classification is referred to, but only 1 of the 4 main headings therein, asphyxiants, is given, and one subheading, anesthetic gases, under their Group III. Carbon monoxide, the carbonyls, and hydrogen sulphide are the only gases included, and benzol and its homologues and trichlorethylene (the formula for which is wrongly given) are the only volatile solvents. Lung changes found in welders' and dyeworkers' cancer are included in this chapter.

The rapid increase in both the numbers of volatile solvents used and in uses therefor, and in discussion of their toxicity in recent literature, warrants more extended references to this group.

The growing importance of industrial dermatoses is indicated by the table and graph presented, but the only conditions discussed specifically are bakers' dermatitis and chrome dermatitis. No reference to the value of patch testing in diagnosis appears.

H. S.

THE MACHINERY OF THE BODY. By ANTON J. CARLSON and VICTOR JOHNSON, The University of Chicago. Pp. 580; 187 illustrations. Chicago: The University of Chicago Press, 1937. Price, $4.00.

ONE of the most difficult problems in education is to present in simple language the elementary facts of a complicated subject such as physiology without distorting these facts. The authors have solved this problem and have consequently established their reputation as teachers on as high a plane as that they have attained in original research. The subject matter is presented with admirable simplicity and clarity and is illustrated by excellent diagrams. Excellent generalizations are made which enable the student to compare, for instance, inhibition in the heart with that in the nervous system. The functions of the endocrine glands are well described with all the clarity possible with our present knowledge. The history of each subject is sketched in an interesting manner and references are given to some books of general interest.

H. B.

Syphilis. The Next Great Plague To Go. By Morris Fishbein, M.D. Pp. 70; illustrated. Philadelphia: David McKay Company, 1937. Price, $1.00.

With the campaign that the Surgeon-General of our Public Health Service is now urging against syphilis, small inexpensive handbooks for the laity are useful adjuncts and, incidentally, should have an excellent sale. Such a booklet from the editor of the *Journal of the American Medical Association* should command especial attention and it is hoped that many will get from it some idea of the cause of the disease, how it is spread, its symptoms, and how it is diagnosed, treated and prevented. The very prominence of the author, however, makes it extra necessary that, once embarked on the venture, he take the necessary time from his busy schedule to write an accurate, balanced presentation. We do not feel that this has been the case: In the first 14 of the 70 pages there is "meat" in less than one; saving here would have permitted a much less inadequate statement in vitally important parts, such as the tertiary stages, the cardiovascular system, paresis, tabes dorsalis, prophylaxis and so on. As examples of material that one would wish to see differently presented: The illustration of Hutchinson teeth is far from typical; interstitial keratitis should not be regarded as "the most characteristic signs of syphilis" at birth; the causative organism is pale-staining, not pale; it is not generally accepted that Columbus' sailors brought syphilis to Europe. A practitioner friend complains that the section on treatment is not as clearly set forth as even a booklet of this size should permit, and that it is incorrect to say that those who react badly to drugs constitute the 10% of incurables. At least a few references to guide toward fuller reading would be helpful. Altogether let us hope that it will be a better "handbook for everyone," or a careful revision of this one, that will be in the forefront of the present campaign.

E. K.

Appendicitis. A Clinical Study. By W. H. Bowen, Hon. M.A. (Camb.), M.S. (Lond.), F.R.C.S., Hon. Surgeon to Addenbrooke's Hospital, Cambridge; Hon. Consulting Surgeon to Royston County Hospital; Examiner in Surgery, University of Cambridge, etc. Pp. 202. Cambridge: The University Press, 1937. Price, $2.50.

This interesting little monograph is, as the author intended it to be, essentially a clinical study. It aims to give the student and practitioner an outline of the common varieties of disease of the appendix. There are 11 chapters, beginning with etiology, and including diagnosis, treatment and complications. Subacute and chronic appendicitis are discussed. The relationship of purgation to perforation has been stressed. The association of stercoliths with appendiceal obstruction and the part which obstruction plays in the progress of the disease are briefly, but ably, reviewed, and the author states "It is clear that the etiologic factor in the severe grades of appendicitis is the stercolith." Paraumbilical or transverse abdominal pain passing to the right iliac fossa he believes to be the most important single finding in the differential diagnosis. The section on treatment is well written. The various viewpoints in regard to conservative *versus* immediate operative treatment in the late cases are thoroughly covered. The author prefers Battle's incision in acute appendicitis. A very interesting chapter is that dealing with chronic appendicitis. The author states that "provided that there is careful analysis of the past history, signs and symptoms and any collateral investigations which seem necessary, the figures suggest that surgical treatment can prove successful in a high percentage of cases." This little volume will be cordially received, as well it should be.

I. R.

Russian Medicine. (Vol. XX of Clio Medica.) By W. Horsley Gantt, M.D., Johns Hopkins University School of Medicine; formerly Chief of Medical Division, American Relief Administration, Leningrad Unit (1922-1923); Collaborator in Pavlov's Laboratories (1925-1929). Pp. 214; 12 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $2.50.

The author divides the history of medicine in Russia into four periods: 1, The primitive period, which extended to the time of Peter the Great; 2, the reign of Peter, during which he founded hospitals and medical schools, and sought to introduce western medicine into his country; 3, the rise of independent Russian medicine in the nineteenth century; 4, state medicine under the Soviet régime.

During the primitive period there was no organized medical education in Russia. The people depended for their medical care on witches and wizards, seers and wolfmen, and all treatment was either based on magic, charms, incantations, prayers, etc., or purely empiric by means of herbs, steam baths, bloodletting, etc. There were no hospitals except a few infirmaries attached to monasteries. Foreign doctors occasionally came to Russia, generally sent by some potentate as an act of courtesy to the tsar; but they remained at Court, and only performed their professional duties to the tsar and his entourage. Peter the Great made strenuous efforts to introduce western medicine in his country. He established medical schools and hospitals and imported teachers. Among other things he purchased the celebrated anatomic museum of Ruysch, and along with it the secret of the Dutchman's method of injecting specimens, and he sent Russian students abroad to study medicine. The enlightened Empress Catherine II did much to elevate the status of Russian medicine, especially when she brought the Englishman, Dimsdale, over to introduce inoculation for smallpox. She also greatly aided the furtherance of medical education by enlarging the scope of the medical schools. During the third period, the nineteenth century Russian medicine made great strides. Great hospitals were established, the medical schools flourished, especially the Military Medical Academy at Petersburg, to which was attached a medical library which Garrison ranked as equal with that of the British Museum and the Surgeon-General's in Washington. Much of this progress must be attributed to some of the really great men whose work won international renown. Sir James Wylie, a Scotchman, who came to Russia as physician to Prince Galitzin in 1790, organized a splendid army medical service and built up the famous Military Medical Academy; Karl Ernst von Baer, the founder of modern embryology; Pirogov, one of the greatest military surgeons of all time; Botkin, the great clinician who did so much for the study of clinical pathology, were worthy predecessors of Mechnikov and Pavlov. The author names many other famous scientists and practitoners who raised Russian medicine during this period to its greatest heights.

The author draws from personal observation a terrible picture of the famine in Russia in 1920–1921, when human flesh was sold in markets and members of families killed their own blood relatives for food. He concludes his work with a valuable and apparently impartial review of the state of Russian medicine under the Soviet government.

This little book presents in concise form an excellent picture of the development of medicine in a great country which has only become civilized in a comparatively few hundred years. It contains a number of excellent illustrations, and a most useful table of comparative chronology. The author is well qualified for his task having served in Russia as a member of the American Relief Administration in 1922–1923, and worked with the lamented Pavlov for five years. He has performed a difficult task in a most able manner.

F. P.

Recent Advances in the Study of Rheumatism. By Frederic John Poynton, M.D., F.R.C.P. (Lond.), Consulting Physician, University College Hospital and the Hospital for Sick Children, Great Ormand Street; and Bernard Schlesinger, M.A., M.D. (Camb.), F.R.C.P. (Lond.), Physician to Children's Department, Royal Northern Hospital; Physician to Out-patients, Hospital for Sick Children, Great Ormand Street. Pp. 380; 51 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $5.00.

This is a review of current trends of thought in the study of rheumatism, including a consideration of etiologic and predisposing factors, pathology and treatment. The authors, who have had extensive clinical and experimental experience, have presented a reasonably coherent and complete picture of arthritis in childhood and chronic arthritis in the adult. Their critical viewpoint recognizes that many more fundamental facts are needed before a completely satisfactory therapeutic regimen can be devised. Yet their attitude toward therapeutic measures is pragmatic, maintaining an open mind toward the utility of measures not yet fully understood.

The book first deals with acute rheumatic disease in children, then with chronic rheumatism. The first portion presents a detailed description of the underlying pathology, though the precise nature of the responsible agents is still a matter of debate. The blood and tissues seldom yield viable microörganisms, and these often form different strains; though the blood serum may show high concentration of antibodies against streptococci, this evidence is not sufficiently specific to implicate any single strain. Furthermore, relapses may occur when the level of circulating antibodies is at its height. It is suggested that the most probable explanation is that streptococcal infection lowers the defense against a virus, because virus bodies are found in pericardial fluids; the lesions are similar to those produced in known virus diseases. The possibility that allergic phenomena are responsible is held to be plausible only. The use of various drugs is described, although the full mode of their action is unknown.

The second half of the book is devoted to chronic rheumatism. The many pathologic features and symptoms that acute rheumatism and chronic rheumatoid arthritis have in common, such as nodules and evidence of infectious factors, are developed. Even the older osteoarthritic with his lesser degree of systemic reaction, his predominant features of degenerative processes, is regarded as expressing the same or allied causes as are present in his younger fellows. The ill-defined factor of tissue age determines in a large measure the contrasting features. This view is contrary to the belief of others who regard the hypertrophic arthritic as presenting merely the effects of age and traumata. The authors regard the pathologic changes in hypertrophic arthritis as additionally reflecting the activity of some active infective factor.

The authors believe that etiologic inquiries require recognition of the extra-articular features of chronic arthritis. Poynton would visualize the subjects of the disease as though bare of organs and composed of bloodvessels, lymphatics and nerves only, with their surrounding network of connective tissue. The "Poyntongram" of this connective tissue skeleton of the rheumatics shows deviations from normal for it is in this system that the first pathologic changes appear. Disturbances in the connective tissues are followed by interferences in the function of the "noble" organs. In joints the changes in the connective tissues are recognized as arthritis. In addition to the articular manifestations usually recognized, attention is directed to the extra-articular expressions, including muscle atrophy, which is more than that due to simple disuse, and to neurovascular phenomena. The latter are regarded as important along with irritants and traumata in the production of osteoarthritic pathology. It is further emphasized that this connective tissue bony skeleton is not a static structure, but that there is an ebb and flow of its material components that makes it susceptible to the influence of toxic, metabolic and psychic factors.

The writers regard infectious foci as significant in providing noxious agents detrimental to the general welfare of the host, but not as as necessary first cause of the disease. A conservative attitude toward eradication of infected organs is therefore advised.

The authors' view, that metabolic studies have contributed little to the understanding of rheumatism, appears to the Reviewer to indicate a mistaken significance of the metabolic phases of rheumatism. The conventional outlook is based upon a cursory review of the fact that purine metabolism is *not* systemically disturbed, that lactic acid, the acid-base balance and inorganic salt metabolism are not uniformly deviated from normal, and that the carbohydrate tolerance in arthritis is not "specifically" abnormal.

In discussing protein metabolism no mention is made of its relation to the anemia, the local increases of metabolically inactive fibrous tissue and the reduction of serum albumin which the arthritic often presents. Yet these are more obvious phases of disturbed nitrogen metabolism than is a modification in the levels of circulating end products such as uric acid, and urea. The former deviations from normal represent, along with the degeneration of cartilage and modification in the matrix of bone, some of the significant changes of the protein components of the body. No mention is made of lowered cholesterol in atrophic nor of elevated cholesterol in hypertrophic arthritis, nor of the blood plasma volume increase in the atrophic as a phase of disturbed water metabolism. No mention is made of the ebb and flow of tissue water during periods of changing degrees of stiffness and swelling. However, even though the authors overlook several features of disturbed metabolism, sufficient data are presented to demonstrate the limitations of simple hypotheses regarding the etiology and nature of rheumatism.

The endocrine system is regarded as involved in greater or lesser degree in the production of some phases of the symptomatology such as the vasomotor phenomena which may underlie the predisposition of the tissues to rheumatism. No single component of the endocrine system is wholly responsible for the full picture even in so-called climacteric arthritis, in the sense that thyroid dysfunction is responsible for myxedema. The authors point out that skin involvement is so frequent as to constitute an integral part of the disease. They are optimistic as to the treatment of chronic rheumatics, having confidence that an accurate diagnosis, an avoidance of new "cures," and a reliance upon systemically operative measures will favor the recovery of the patient. Diet is handled as an individual problem for each patient. The use of grossly imbalanced rations is deprecated and the authors epitomize their whole attitude toward therapy in the following facetious but hardly critical summary: "stung by bees, giddy with histamine, sore from sulphur injections, itching from gold, short of food and threatened with wholesale dental extractions, we prefer the pleasanter forms of treatment rather than to prolong our rheumatic existence on even the most modern principles."

Brief chapters on Physiotherapy by Frank Howett, C.V.O., M.D., F.R.C.P., and on Surgical Treatment of Chronic Rheumatism by Eric I. Lloyd, M.B., B.Ch., F.R.C.P., are appended. In both of these the same perspective is maintained, emphasizing the necessity for individualized application of the various procedures at appropriate times and with due regard for the patient's general condition.

C. S.

THE CEREBROSPINAL FLUID. By H. HOUSTON MERRITT, M.D., Assistant Professor of Neurology, Harvard Medical School; Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital, and FRANK FREMONT-SMITH, M.D., formerly Assistant Professor of Neuropathology, Harvard Medical School; formerly Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital. With a Foreword by JAMES B. AYER, M.D. Pp. 333; illustrated. Philadelphia: W. B. Saunders Company, 1937. Price, $5.00.

THE authors of this interesting monograph are ideally suited to have written it. They have spent considerable time in a study of the subject and have made worthwhile contributions to medical knowledge in this field. The monograph was not written from a single point of view. Rather have the authors presented a group of facts. Many case histories with proven diagnoses are included to illustrate the points which are made. Laboratory and clinical findings are clearly presented. There are 8 chapters, and in addition an excellent bibliography, and index of authors and subjects. The anatomy and physiology are briefly but adequately reviewed. The chemistry and pathologic physiology are thoroughly covered and many tables of data are included. The technique of lumbar and cistern puncture with clinical interpretations is well written and will prove of considerable value. The section on cerebrospinal fluid syndromes is the most extensive the Reviewer has found. The present volume might well be compared with Kafta's "Die Zerebrospinalflussigkeit" which was published in 1930. The many typographical errors found in that volume are absent in the present one. The present volume is more practical, and of course more easily used by the English-speaking portion of the medical profession. It should prove to be a constant reference for all those interested in this very important field.

I. R.

LANE MEDICAL LECTURES: THE MECHANISM OF HEAT LOSS AND TEMPERATURE REGULATION (Stanford University Publications, Medical Sciences, Vol. III, No. 4). By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital, New York. Pp. 95; 41 illustrations. Stanford University: Stanford University Press, 1937. Price, Paper, $1.50; Cloth, $2.25.

THESE lectures provide an interesting review of the classical work on heat production and direct calorimetry on man, in which the author has played such an important rôle. He points out that the presence of a causal relationship between surface area and basal metabolism is uncertain, since the basal metabolic level can be maintained over a fairly wide range of conditions of different cooling capacity. Yet the rule relating the actual observed metabolism to the total surface area (or the relatively smaller effective surface area) in various species is found to hold with a few exceptions, which are noted.

The student reader may find difficulties in a terminology which does not always conform to ordinary usage. Thus the author states "the insensible perspiration includes not only weight loss due to vaporization—but also the slight excess in the weight of carbon dioxide eliminated over the oxygen absorbed." This is not the common usage of the term "insensible perspiration" and a similar unorthodox use of terms is again exemplified when he describes Hardy's experiments on temperature sensation. He says these establish "the laws of summation which have practically ruled out the factor of facilitation." Most physiologists would state that these experiments indicated a spatial summation of sensations by a process probably actually dependent on central facilitation.

H. B.

THE MANAGEMENT OF THE PNEUMONIAS. For Physicians and Medical Students. By JESSE G. M. BULLOWA, B.A., M.D., Clinical Professor of Medicine, New York University College of Medicine; Visiting Physician and Director Littauer Pneumonia Research Fund, Harlem Hospital; Visiting Physician, Willard Parker Hospital. Pp. 508; 142 illustrations. New York: Oxford University Press, 1937. Price, $8.50.

Too long has there been a tendency in some parts of the profession to rest content in diagnosis with the attempt to distinguish between lobar and bronchopneumonia. In this book the author has collected in relatively brief form the currently accepted ideas concerning the biologic nature of the pneumonias. Adequate emphasis is given to the importance of recognizing the pneumonias as a group of specific bacterial diseases which careful bacteriologic study alone can differentiate. A useful discussion of the Neufeld method of pneumococcus typing is included. Reference is made to the work of the late Georgia Copper in identifying specifically Types IV to XXXII which in the past were customarily designated as "Group IV." Many charts and tables illustrative of the higher pneumococcus types as well as the more common types are shown. The more frequently encountered organisms, exclusive of pneumococci, that may produce pneumonia are dealt with in sufficient detail.

The management of the pneumonias is discussed as much as the subject at present allows from the standpoint of etiology. Seventy-nine pages are devoted to serum therapy and 69 to oxygen therapy. Among other topics included are general treatment, sedation, glucose, chlorides, quinine and quinine derivatives, digitalis, artificial pneumothorax and the more recently introduced rabbit antipneumococcus serum.

The format is attractive and the material presented should aid in lowering the present pneumonia mortality in the United States by diffusing the knowledge that is now available concerning the importance and feasibility of early specific diagnosis and treatment. L. C.

DER PSYCHISCHE RESTITUTIONSEFFEKT. Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion. (The Psychic Restitution Effect. The Principle of Restoring the Fatigued, Exhausted or Diseased Function by Psychic Influences.) By DR. MED. OTTO LÖWENSTEIN, vorher ordentl. Professor und Direktor des Pathopsychologischen Instituts der Universität Bonn sowie leitender Arzt der Rheinischen Provinzial-Kinder-Heilanstalt für seelich Abnorme in Boon. Nyon (Schweiz), Klinik La Métairie. Pp. 92; illustrated. Basel: Benno Schwabe & Co., 1937. Price, Francs suisses, 8.00.

THIS little monograph, illustrated by a number of impressive graphs, tells in plain language a story which should be interesting equally to physiologists, psychologists, neurologists and syphilologists. The pupillary reflex is recorded cinematographically under controllable conditions of light stimulation. When the pupil is stimulated for 1 second periods, with intervals of 2 seconds, the reaction decreases gradually, and eventually the pupil fails completely to react to light. Sluggishness of contraction and dilatation, increase of latency of contraction, later its replacement by initial and finally by paradoxical dilatation mark the path of the fatigue of the pupillary reflex. Seven well-characterized stages of the fatigue phenomenon are differentiated. They follow one another in regular sequence but at an individually varying time interval. The appearance of fatigue is accelerated by noxious conditions, such as blue light, by increases in the frequency of stimulation, in the duration of the single stimuli and in their strength. With each subsequent experiment the restitution time becomes longer and the quantity of residual fatigue increases. All these observations prove that in fact the central function is exhausted and that adaptation does not play a part in the phenomenon. The pupillary reflex which has become completely fatigued and has disappeared can be restored immediately by sensory stimuli or verbal suggestions leading to fear or painful sensations or to joyful emotions. While the latter remain effective in restoring the fatigued pupillary reflex as long as they are able to produce a pleasant sensation, the stimuli accompanied by negative emotions gradually fail to elicit the phenomenon of psychic restitution. The cinematographic record shows that the reaction of the fatigued pupil to light, following a sensory stimulus, passes backward through the same seven stages which characterize the fatigue phenomenon. The "defatiguing" effect of sensory stimuli were shown also in the slightly abnormal patellar reflex, fatigued by 4 previous stimuli, in a patient with initial tabes. The effect of psychic restitution upon the pupillary reflex is present also when the reflex is partially damaged by disease. This is true in syphilitics as well as in postencephalitic Parkinsonians. The sluggish reaction in the former, the tonic in the latter regains its fast, prompt and extensive reflectory movement after psychic or sensory stimulation. No restitution effect can be produced once the pupil becomes completely fixed, even though the pupil may still enlarge the psychic influences or painful stimuli. These two phenomena, therefore, seem to be independent of each other. The degree to which pupillary function made abnormal by organic disease can be temporarily restored by psychic restitution gives an indication as to how far the function can and should be revived by treatment. Observation of a person with a Horner syndrome suggests that the appearance of psychic restitution depends on the integrity of the sympathetic innervation. It is possibly a general rule that the vegetative functions are kept alive by continuous restitution through sympathetic stimuli.

This booklet, full of well-organized facts and void of undue hypotheses, makes fascinating reading. F. L.

PRACTICAL PROCTOLOGY. By LOUIS A. BUIE, A.B., M.D., F.A.C.S., Head of Section on Proctology, The Mayo Clinic; Professor of Proctology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 512; 152 illustrations (2 in color). Philadelphia: W. B. Saunders Company, 1938. Price, $6.50.

THE author's book is well named. From his rich experience he has written a book filled with practical and useful information concerning his special subject. Psychologic aspect of the attitude of the physician and patient in making anal and rectal examinations and in carrying out the necessary treatment are first discussed. After a description of the technique of examination, the author considers the anatomy of the anus and lower rectum. His chapter on pre-operative and postoperative care is written with a background of handling patients and might well be followed by many general surgeons who have occasion to perform operations on the lower rectum and anus. He then discusses in detail the various diseases of this region. The book ends with a chapter on diets and various prescriptions which he has found useful in his work. It is beautifully illustrated throughout and is one which should be invaluable to surgeons and internists alike, whether diagnosis or treatment of the lesions of this region is necessary in practice.

The single criticism to make of the book is that some of his recommended treatments are not those which would be found practical in the ordinary practice of proctology. For instance, in his chapter on anal fissure he recommends a more radical treatment than is usually found necessary and no mention is made of the value of oil-soluble anesthetics in this condition. In the chapter on anal pruritus his procedure of infiltration of alcohol sufficient to produce a slough is rarely necessary. A complete and beautifully illustrated chapter on ulcerative colitis gives in detail ideas which he and Dr. Bargen have previously published.

The book is written throughout in the author's forceful manner, the use of the first person emphasizing the personal experience of the author with the diseases and treatments which he is discussing. Anyone who is at all interested in proctology will count this book as among his most valuable.

L. F.

THE POSTMORTEM EXAMINATION. By SIDNEY FARBER, M.D., Associate in Pathology, Harvard Medical School; Pathologist to The Infants' Hospital and the Children's Hospital, Boston. Pp. 201; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $3.50.

THIS book is designed for ready reference as a guide to an adequate method of performing autopsies. Though there is already in English a very satisfactory inexpensive volume of this type, by Coman, this work will be useful to beginners in pathology and to those who perform but occasional postmortems. The material is clearly and fully presented. The drawings are of considerable aid in delineating actual technique. The incorporation of special procedures and methods for infants and children is worth while.

S. L.

VITAMINS IN THEORY AND PRACTICE. By LESLIE J. HARRIS, Sc.D., D.Sc., Nutritional Laboratory, University of Cambridge, and Medical Research Council. Pp. 242; 66 illustrations and 44 tables. Second edition. Cambridge: University Press, 1937. Price, $3.00.

IF the numerous small, semipopular books on the vitamins are to keep pace with a rapidly accumulating literature, both clinical and experimental, new editions will have to be published frequently. A second edition of this excellent compendium within two years of the first edition has, so far as possible, brought the information up to date. It tells the whole vitamin story which is always of fresh interest and uses it as a text to philosophize about the great scientists as the catalysts of scien[illegible] The illustrations are many and varied, making visible the [illegible] in man and in experimental animals, the great scientists and lay experimenters who revealed the existence of the vitamins, and the substances themselves in their crystalline forms. The clinical applications of the vitamins are discussed at length and there is a supplementary section on dietetics that might make a good pamphlet to circulate separately. Presented originally in lecture form, the text has preserved an easy, conversational tone.

E. W.

NOT SO LONG AGO. A Chronicle of Medicine and Doctors in Colonial Philadelphia. By CECIL K. DRINKER, M.D., Sc.D., Professor of Physiology and Dean of the School of Public Health, Harvard University. Pp. 183; illustrated. New York: Oxford University Press, 1937. Price, $3.50.

ELIZABETH DRINKER, the author's great great grandmother, kept a celebrated diary with almost daily entries from 1758 to 6 days before her death in 1807. Staying much at home, mother of 9 and grandmother of 29, she naturally filled many pages of her 36 home-made volumes with accounts of family illnesses and references to the physicians who attended them. John Redman, Adam Kuhn, Rush, Shippen, Physick and other worthies live again in these pages of excerpts of medical interest from the voluminous record. Childbearing, tuberculosis, smallpox, dysenteries, malaria and yellow fever receive chief attention; but a wise selection that avoids tiresome repetition gives, as the most vivid picture of all, the domestic medicine of a cultured household over an important transitonal period of medical history. Though the Drinkers inevitably figure prominently, the author of this volume does not hesitate to digress into general fields, such as the development of forceps and male midwives in obstetrics, Lady Montague and inoculation for smallpox, and the progress of medicine in the 19th century. (Here one might well question the author's dictum that "nowadays our large cities are healthier places than is the country.") Clearest of all emerges from her own record the doughty figure of Elizabeth Drinker herself, faithfully giving daily purges, injections, vomits, glysters and blisters to her loved ones as directed; yet with intelligence enough early to advocate vaccination over inoculation and independence enough on occasion to differ from Dr. Redman in his diagnoses. Our ancestors' constant struggle with disease and their comparative helplessness in dealing with it seldom has been more strikingly portrayed than in these humble pages. "Not So Long Ago—But What a Difference" is the amended title that will suggest itself to many a reader of this illuminating record and perhaps that is just what the author intended. E. K.

A TEXT-BOOK OF MEDICAL BACTERIOLOGY. By R. W. FAIRBROTHER, D.Sc., M.D., M.R.C.P., Lecturer in Bacteriology, University of Manchester; late Research Fellow in Bacteriology, Lister Institute, London. Pp. 437; 12 illustrations and 32 tables. St. Louis: The C. V. Mosby Company, 1937. Price, $4.50.

IN the space of 437 pages it is impossible to present an exhaustive treatise on all phases of bacteriology. The author, therefore, limited himself to the application of bacteriology to medicine and public health. Not trying to save space by presenting only the well-established facts and conclusions, the author considers various controversies and problems which are confronting bacteriologists and medical men. The general plan for considering bacterial diseases was: 1, The identification of pathogenic bacteria; 2, the immunologic diagnosis of disease; 3, the detection of individuals susceptible to the disease; and 4, specific prophylaxis and therapy. The book is well printed, easily readable and beautifully bound. It is very good for beginners or those desiring an elementary treatise, but inadequate for advanced students or as a reference book. No references are cited and there are very few tables and illustrations. H. M.

A PEDIATRICIAN IN SEARCH OF MENTAL HYGIENE. By BRONSON CROTHERS, M.D., Assistant Professor of Pediatrics, Harvard Medical School; Visiting Physician to the Children's Hospital, and to the Infants' Hospital, Boston. Pp. 271. New York: The Commonwealth Fund, 1937. Price, $2.00.

HAVING insight into neurology, this pediatrician realized that if adequate care was to be accorded children handicapped by nervous disorders, proper consideration must be given the educational and emotional elements of each situation. The subject matter is presented under three major headings: Mental Hygiene in the Practice of Medicine, Mental Hygiene in the Teaching of Medicine, and Towards Meeting the Pediatrician's Responsibility. In the last, is a chapter entitled, A Teaching Experiment in Action. Here are grouped children showing neurologic difficulties: 1, Those with acute diseases necessarily treated according to established methods; 2, those with "diseases that are remorselessly progressive," whose care also is a strictly medical matter: 3, children left with some residual physical or mental handicap, which necessitates the assistance of non-medical workers. The "search" is ended. The author is revealed as having understanding of the entire mental hygiene movement and one is convinced that in this realm of endeavor there is need of properly trained pediatricians.

N. Y.

The Diagnosis and Treatment of Sexual Disorders in the Male and Female Including Sterility and Impotence. By Max Huhner, M.D., formerly Chief of Clinic, Genito-urinary Department, Mt. Sinai Hospital Dispensary; Attending Genito-urinary Surgeon, Bellevue Hospital, etc. Pp. 490; 8 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, $5.00.

A treatise that has called forth a fourth edition and 21 reprintings of previous editions hardly needs more than that attention be called to the present opportunity of students of this subject. There is much new material incorporated, and a considerable part of the empirical therapy deleted. Steinach's operation is put in its proper place; as an admirer of Freud, the author gives him just due; the endocrine knowledge of today is too briefly utilized, and one looks in vain for the technique of a spermatozoa count so valuable in estimating the responsibility of the male in a sterile union. The book is exceedingly well written and well balanced, with abundant therapeutic suggestions drawn from the author's long experience in this specific field. A. R.

International Clinics. Vol. IV. Forty-seventh Series. December, 1937. Edited by Louis Hamman, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 Collaborators. Pp. 343; illustrated; 1 colored plate. Philadelphia: J. B. Lippincott Company, 1937.

Of the 23 articles in this volume, 9 are on surgical conditions within the abdomen; the rest are distributed over the fields of Pediatrics, Urology, Endocrinology and Infectious Diseases. The opening article by Spies and Cooper on the diagnosis of pellagra is the most interesting to the Reviewer, Its 5 case reports, characteristic of different types of the disease, and richly illustrated with 21 figures and 1 colored plate, should be of permanent value to many. E. K.

NEW BOOKS.

Alcohol. One Man's Meat. By Edward A. Strecker, A.M., M.D., Sc.D., Professor of Psychiatry, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc., and Francis T. Chambers, Jr., Associate in Therapy, Institute of the Pennsylvania Hospital, Philadelphia. Pp. 230. New York: The Macmillan Company, 1938. Price, $2.50.

Practical Proctology. By Louis A. Buie, A.B., M.D., F.A.C.S., Head of Section on Proctology, The Mayo Clinic; Professor of Proctology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 512; 152 illustrations (2 in color). Philadelphia: W. B. Saunders Company, 1938. Price, $6.50. (Review, p. 547.)

A Textbook of Hematology. By William Magner, M.D., D.P.H., Pathologist, Saint Michael's Hospital, Toronto, Canada; Lecturer in Pathology, University of Toronto, etc. Pp. 395; 23 illustrations, 3 colored plates and 3 charts. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $4.50.

Fractures and Dislocations for Practitioners. By Edwin O. Geckeler, M.D., Fellow of the American College of Surgeons; Fellow of the American Academy of Orthopædic Surgeons. Pp. 252; 213 illustrations. Baltimore: William Wood & Co., 1937. Price, $4.00.

Textbook of Experimental Surgery. By J. MARKOWITZ, M.B. (TOR.), PH.D., M.S. in Experimental Surgery (MINN.), Research Associate, Department of Physiology, University of Toronto; formerly Professor of Physiology, Georgetown University School of Medicine, Washington, D. C., etc. Pp. 527; 330 illustrations. Baltimore: William Wood & Co., 1937. Price, $7.00.

Le Traitement de la Tuberculose Pulmonaire par la Tuberculine. By DR. M. JAQUEROD (LEYSIN). Pp. 43; 2 plates. Lausanne: Librairie Payot et Cie., 1937. Price, Sw. fr., 2.50.

Physicians' Vitamin Reference Book. Presenting to the Clinician a Useful Compendium of the Latest Facts about Vitamins. By the Medical Division, Professional Service Department, E. R. Squibb & Sons. Pp. 126; 10 illustrations. New York: E. R. Squibb & Sons, 1938.

Practitioners should find this handbook of great value. In not too condensed form, it covers the deficiency diseases, in both early and late manifestations, and gives in detail the food and other sources of the vitamins, and human requirements.
E. W.

The Medical Clinics of North America, Vol. 22, No. 1 (Chicago Number—January, 1938). Pp. 264; 42 illustrations. Philadelphia: W. B. Saunders Company, 1938.

St. Thomas's Hospital Reports. Second Series, Vol. II. Editors: PROF. O. L. V. S. DE WESSELOW, MR. C. MAX PATE, assisted by MR. N. R. BARRETT, DR. J. ST. C. ELKINGTON, DR. A. J. WRIGLEY. Pp. 271; illustrated. London: St. Thomas's Hospital, 1937. Price, 7s. 6d.

This second volume of St. Thomas's Hospital Reports, under the new system of including original articles reflecting recent work at the hospital, contains 23 rather brief clinical papers on a wide variety of subjects. There are also abstracts of 28 articles and a list of other publications by members of the hospital staff.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 6. Gonorrhœa to Hydrotherapy. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GRAY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.), F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 650; 89 text illustrations and 7 plates. London: Butterworth & Co., Ltd., 1937. Price, $12 per volume.

Pulmonary Tuberculosis in Practice. A Modern Conception. By R. C. WINGFIELD, B.A., M.B., B.CH., F.R.C.P., Medical Superintendent, Brompton Hospital Sanatorium, Frimley; formerly Tuberculosis Officer, St. Thomas's Hospital. Pp. 122; 25 illustrations and 1 insert (in color). Baltimore: William Wood & Co., 1937. Price, $2.50.

Lectures on the Epidemiology and Control of Syphilis, Tuberculosis, and Whooping Cough, and Other Aspects of Infectious Disease. (The Abraham Flexner Lectures, Series No. 5.) By THORVALD MADSEN, M.D., Director of the State Serum Institute of Denmark, Copenhagen; Chairman of the Health Committee of the League of Nations. Pp. 216; 21 illustrations. Baltimore: The Williams & Wilkins Company, 1937, for Vanderbilt University. Price, $3.00.

A Practice of Orthopædic Surgery. By F. P. MCMURRAY, M.B., M.CH., F.R.C.S. (EDIN.), Director of Orthopædic Studies and Lecturer in Orthopædic Surgery, Liverpool University; Honorary Orthopædic Surgeon, David Lewis Northern Hospital, etc. Pp. 471; 178 illustrations. Baltimore: William Wood & Co., 1937. Price, $5.00.

NEW EDITIONS.

Operative Gynecology. By **Harry Sturgeon Crossen**, M.D., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine, Gynecologist to the Barnes, St. Louis Maternity, and St. Luke's Hospitals, etc., and **Robert James Crossen**, M.D., Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine; Assistant Gynecologist and Obstetrician to the Barnes and St. Louis Maternity Hospitals, etc. Pp. 1076; 1261 illustrations including 3 colored plates. Fifth edition, revised and reset. St Louis The C. V. Mosby Company, 1938. Price, $12.50.

"The seven years since the last edition of this work constitute a period of unusual activity in searching out the fundamentals of gynecologic physiology and structure and in applying such knowledge to the cure of diseased conditions. This intensive study has extended also to our therapeutic resources—old and new, medical and surgical—giving a much better understanding of their possibilities and limitations . . Worthy of emphasis also is the endeavor to found every decision for operation on substantial and clearly understood reasons which justify the risk, and then to reduce that risk to the minimum by critical pre-operative examination and preparation and by effective postoperative care. . . . ." The main object of this work remains "to push the fight against disease by presenting the advances of surgery as applied to the relief of gynecologic diseases in a way which will give practical aid to the surgeon seeking help on these problems." (From senior author's Preface)

Applied Pharmacology. By **A. J. Clark**, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh, formerly Professor of Pharmacology in the University of Cape Town, and later in the University of London. Pp. 678; 83 illustrations Sixth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $5.00.

Practical Bacteriology, Hæmatology and Animal Parasitology. By **E. R. Stitt**, M D , Sc.D., LL.D., Rear-Admiral, Medical Corps, and Surgeon-General, U S. Navy, Retired; formerly Associate Professor of Medical Zoology, University of the Philippines; **Paul W. Clough**, M.D., Chief of Diagnostic Clinic, Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University, etc.; and **Mildred C. Clough**, M.D., formerly Fellow in Bacteriology and Instructor in Medicine, Johns Hopkins University. Pp. 961; 208 illustrations (4 in colors). Ninth edition, rewritten, revised and enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $7.00.

The Compleat Pediatrician. Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By **Wilburt C. Davison**, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital, etc. Pp. 275. Second edition, completely rewritten for the use of medical students, internes, general practitioners, and pediatricians. Durham, N C.: Duke University Press, 1938. Price, $3.75

"This second edition, which has been so completely revised that it might be called 'The Compleater Pediatrician,' was written because of the additional pediatric information which has accumulated during the past four years. The great usefulness of pediatric yearbooks and periodicals is realized as 'only a maker of books can appreciate the labours of others at their true value' (Osler), and they have been freely used However, they merely record the changes in pediatrics, while this revision is an effort to correlate these newer advances with the pre-existing knowledge, and to present an up-to-date digest. . . . . The present edition is an effort to compile and record briefly those *practical* pediatric facts, which though essential, usually slip from memory, it is an attempt to combine in one volume, the information usually found in several, which should be consulted for more complete study. . . . The hope is expressed that this book may serve as 'a ready reminder' to be carried, like a stethoscope, in a physician's pocket or bag (see Chapter XII) to jog his memory on possibilities, but it cannot do his thinking for him." (From the author's Preface.)

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,
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ECTOPIC PREGNANCY.

WHILE ectopic pregnancy is no longer the curiosity it was a generation or two ago, it still holds much interest for the gynecologist as well as for the general practitioner. The treatment of the condition has become well standardized in the average case but in some of the unusual cases there is still room for discussion. Likewise the diagnosis of the case which presents a textbook picture seldom eludes the average practitioner, but in the atypical cases, and there are many of them, the attending physician's diagnostic ability may be severely tested. We do not definitely know why these pregnancies develop outside of the uterus but the theory which has been advanced by Frankel and Schenck[2] is at least interesting. Along with other observers they have demonstrated healthy endometrial tissue in tubal lumina whether or not they were the site of pregnancy. They have found such tissue present at the site of a pregnancy in 87.5% of cases where they have made a careful search and believe that it is present at the outset in 100% of the cases. In 1 case, they found endometrial glands in the decidual tissue, which they believe proves that the decidual reaction was caused by the response of the endometrial elements and not the tubal structure itself. This ectopic endometrial tissue was found in 1 out of 204 normal cases, an incidence of 0.5% which corresponds to the ratio of ectopic to intrauterine pregnancy. According to their theory, all ectopic pregnancies, tubal or otherwise, occur because of nidation of the fertilized ovum in a locus of ectopic endometrial tissue to which the ovum is chemotactically attracted. The fate of the gestation depends upon the amount of endometrial tissue present to undergo the decidual reaction and upon the depth of penetration of the ovum beyond the borders of this decidua. It has been repeatedly stated that a tubal pregnancy may lose its position in the tube and implant itself secondarily elsewhere, continuing its growth in the new site. They do not believe that this is possible because the embryo depends upon the maintenance of a free flow of maternal blood around its chorionic villi. When the trophoblast is confined in decidua, the embryo is nourished, but when the villi break their bounds, they become embedded in blood clot and the embryo is in a short while asphyxiated. They state that it is impossible for an embryo once surrounded by coagulated blood to extricate itself when deposited in a fresh place and recommence its development. Whether tubal rupture or tubal abortion occur the fate of the embryo is sealed from the moment the perifetal coagulation starts. Hence the existence of an ovarian pregnancy, an abdominal pregnancy, or an intraligamentous pregnancy cannot follow on its extrusion from the tube but exists because it begins its development primarily in these sites.

Diagnosis. In discussing the diagnosis of tubal pregnancy, Mathieu[7] is of the opinion that the typical history of a missed menstrual period, sharp lancinating pain in the lower part of the abdomen, followed by dizziness, weakness and faintness, soreness in the abdomen, and bleeding from the vagina, represents only a small percentage of all the cases of tubal pregnancy. The others, not typical, are at times very difficult to diagnose. There are patients with symptoms and complaints so minor or so bizarre that the physician may actually wonder whether or not there is anything wrong at all. There is no doubt that many cases go undiagnosed and that the effects go unnoticed. For those who like the finer points of diagnosis, he presents 8 types of pain which are met in this condition, all explainable on a pathologic basis: 1, Acute lancinating pain coincident with rupture of the tube; 2, dull, constant pain associated with stretching and slow tearing of the tube before rupture; 3, crampy, almost constant pain caused by peristalsis of the tube and dilatation of the distal end of the tube during a tubal abortion; 4, soreness and tenderness of the entire abdomen caused by irritation of the peritoneum from the escaped blood; 5, phrenic or shoulder pain produced when the blood gets high in the abdominal cavity, under the diaphragm, and irritates the phrenic nerve endings (this pain is felt on either or both sides of the neck); 6, pain elicited by the deep muscle resistance that results when the palpating fingers sink deeply enough to cause pressure on the parietal peritoneum. When there is free blood in the abdominal cavity, palpation of the anterior abdominal wall is almost pathognomonic. The abdomen is usually not distended. There is generalized pain or soreness over the entire abdomen and with fairly light palpation the fingers will sink part way into the abdominal wall without resistance, only to be met by a rather doughy resistance as the fingers sink deeper. This tenderness is quite unlike that of the acute firm resistance and tenderness one finds in acute appendicitis with peritoneal involvement; 7, pain produced by moving the cervix or fundus; 8, generalized pelvic tenderness and pain produced by the palpating fingers. It should be realized that all of these pains are not present in every case but their enumeration should make us think of them. To the Reviewer, the pain produced by motion of the cervix during pelvic examination, while not stressed much in most textbooks, is of extreme diagnostic importance and is seldom absent. This pain is usually excruciating and is rarely found except in ectopic pregnancy.

In regard to pregnancy tests such as the Aschheim-Zondek or any of its modifications, it should be remembered that a positive test means that there is living chorionic tissue present, hence the test can be positive even when the fetus is dead. A negative test merely means that there is no living chorionic tissue present, therefore the test will not exclude the diagnosis of ectopic pregnancy. Moreover the test, if positive, gives no indication as to whether the pregnancy is intra- or extrauterine. In regard to a diagnostic aspiration of the cul-de-sac, Mathieu does not consider it entirely harmless and he does it only when the presence of fluid in the pelvis is obvious, under which conditions it is often an important diagnostic procedure. The sign described by Cullen is the presence of an ecchymosis in the tissues of the umbilicus. There must be not only an actual hernia but also some break in the integrity of the peritoneum at this site so that the blood can actually reach the subcutaneous tissues. He has found the sign to be extremely rarely present and that is also the experience of the Reviewer. (The Cullen sign is rarely seen in early cases.) The urobilinogen and icterus index tests are of value in determining the presence of a hematoma or of blood in the process of absorption and hence might point to a ruptured ectopic pregnancy. The blood sedimentation test is of little direct diagnostic value, a rapid rate usually rules out ectopic pregnancy while a slow rate is infrequent in the presence of a pelvic abscess or salpingitis. He has used hysterosalpingography in several cases as an aid in diagnosis with practically 100% correct diagnoses. He has been able to visualize a tubal abortion and has established what seems to be a pathognomonic Roentgen ray sign for a tubal pregnancy in the midportion of the tube. In cases of tubal pregnancy aborting from the distal end of the tube, the injected oil enters all the crevices between the aborting pregnancy and the walls of the distal end of the tube in such a way that it literally drapes itself about the mass and allows the oil-covered mass to be visualized by the Roentgen rays. In his cases of tubal pregnancy in the midportion of the tube, the injected oil went down to the site of the pregnancy and, because this site was well sealed off, ended abruptly and showed in a characteristic shadow. While this procedure should not be done routinely, if done carefully it should be harmless and if both tubes fill normally, at least ectopic pregnancy can be ruled out. This test should be of particular value in differentiating ectopic pregnancy from the internal hemorrhage associated with a ruptured ovarian follicle or corpus luteum, in which differentiation no other tests are of much assistance.

Buschbeck[1] states that the diagnosis of ectopic pregnancy presents no difficulty when the usual signs of a ruptured gestation sac are present such as internal hemorrhage, hematocele and peritoneal shock. In those cases in which the pregnancy runs a more chronic course there may be considerable difficulty in diagnosis. In such cases the menstrual history may be the only diagnostic sign of importance. He has investigated the history in 143 cases and found that in 141 of them it conformed to one of three types. In the first type the history is only that of amenorrhea and there were 17.5% of the cases in this group. The second type, which was that shown by over half (58%) of the patients, consisted of a period of amenorrhea followed by continuous bleeding. In the third type, comprising 23.1% of the cases, the history was that of an atypical period at approximately the usual time, either more or less bleeding than usual, then a free interval followed by continuous bleeding. Therefore in any patient who exhibits any one of these three types, particularly if accompanied by pelvic discomfort, a pelvic examination should be done and if no definite diagnosis can then be made, the patient should be kept under observation until the diagnosis becomes clarified.

Another study of the diagnostic value of the menstrual history based on a series of 153 cases has been made by von Graff and Brown.[12] In 9% of the cases irregular bleeding over a period of several months barred definite conclusions. In 38% the bleeding followed definite amenorrhea, but in 53% there were no previous menstrual disturbances. In these cases, the bleeding started either during the intermenstruum or at the expected time, presumably as a normal period, but was unduly prolonged. The latter type of bleeding is very misleading, especially if there are no local symptoms. Observation of the bleeding often gives definite clues. At the onset there may be copious bleeding with the expulsion of clots and tissue but this may occur with intrauterine abortion and only histologic examination can differentiate between the two conditions. In uterine abortion, the blood remains red but in ectopic pregnancy the discharge gradually assumes a dirty brown color which is almost pathognomonic. As important as the color is the duration of the bleeding. In intrauterine abortion, since the pregnancy is not far advanced, the flow usually stops with the spontaneous completion of the miscarriage or after bed rest and the use of oxytocics, but in tubal abortion the discharge goes on regardless of treatment. The hemoglobin and red cell count do not often suggest intraäbdominal bleeding but the white cells are frequently increased to such an extent as to suggest infection which explains the frequent erroneous diagnosis of acute pelvic inflammation. The temperature may or may not be elevated but is seldom over 101° F. but the pulse rate is high. This is to be expected with marked anemia or shock but may be present even when the patient's general condition is good due to peritoneal irritation by the blood in the peritoneal cavity.

In ectopic pregnancy, according to Siddall and Jarvis,[10] incorrect diagnoses occur in from 15 to 40% of the cases and they recommend the performance of uterine curettage as an aid in making the diagnosis. It will be remembered that in intrauterine pregnancy the chorion forms in the uterus while in ectopic pregnancy only decidual tissue is found there, the chorion, being of ovular origin, will form wherever the ovum lodges. In a series of 38 cases of proved ectopic pregnancy with available specimens of endometrium, intact decidua alone was present in all cases with abnormal bleeding of 10 days or less and in a considerable proportion of those with more prolonged bleeding. The absence of decidual reaction is not reliable evidence against ectopic pregnancy, but if chorionic villi are also absent, the findings may be of value in ruling out uterine abortion as a cause of bleeding. The performance of such curettage in a suspicious case is not unduly dangerous and the finding of intact decidua without chorionic villi is strong presumptive evidence of the existence of extrauterine pregnancy. (The diagnosis can usually be arrived at by other means and hence diagnostic curettage is rarely necessary.)

It is not unusual in certain cases of intrauterine pregnancy that have exhibited spotting or bleeding, accompanied by some pain in the lower abdomen, for the surgeon to subject the patient to a laparotomy because of the fear of the existence of an ectopic pregnancy and it must be admitted that in some cases this is the safest plan to follow. In such instances Hope[5] feels that peritoneoscopy is of value for by this procedure we have a method of actually seeing the uterus, tubes and ovaries. It can be done under local anesthesia and requires but 24 hours of hospitalization. Should the peritoneoscope determine that the pregnancy is within the uterus, the danger of aborting is less likely than following a laparotomy. The patient may return home for expectant treatment, with a saving of several weeks of hospitalization for postoperative care and of much discomfort, not to mention conservation of finances. If, on the other hand, an ectopic pregnancy is seen, immediate laparotomy is done and both the physician and the patient are saved time, worry and the risk of delay. In the performance of peritoneoscopy, the technique which he recommends consist of preparing the abdomen as for laparotomy. The bladder must be catheterized immediately before the examination because a full bladder may obscure the view of the pelvis. Local anesthesia, using 1% novocaine, is infiltrated in a wheal formation, starting at a point in the midline about 4 cm. below the umbilicus and taking in all layers down to and including the peritoneum. Should there be a scar from a previous laparotomy, the site for entering the abdomen with the trocar is chosen well away from it, to avoid any adhesions that may be present. After anesthesia is established, a stab wound, 1 cm. long, is made through the skin and rectus fascia. A small trocar is inserted into this and pushed through the peritoneum into the abdominal cavity. A pneumoperitoneum is then created by injecting air into the peritoneal cavity through the trocar using a small manometer bulb. The small trocar is withdrawn and the trocar sheath inserted into the peritoneal cavity through the stab wound with safety, as the intestines are held down by a cushion of air. The trocar point is removed from the sheath and a visual telescope is inserted. Any air that has escaped is now replaced, as air is essential for good visualization as well as a means of displacing the viscera. A general rapid survey of the peritoneal cavity is then made, going completely around the clock. The patient is then placed in the extreme Trendelenburg position which allows the intestines to fall back out of the pelvis and a detailed examination of the uterus and adnexa may be made. This is greatly facilitated in many cases by an assistant placing two fingers in the vagina and manipulating these organs. By this means the uterus can be pushed up into view if dropped far back in the pelvis, a prolapsed ovary brought into sight, and adhesions and fixation of the uterus demonstrated. On completing the examination, the patient is replaced in the horizontal position, the air is allowed to escape from the peritoneal cavity through the instrument and the latter is removed. If an ectopic gestation or hemoperitoneum is found, immediate operation is then performed. The skin is again prepared, new drapes are placed and the stab wound is incorporated in the usual laparotomy incision. If on the other hand there is no indication for immediate surgery, a single stitch or clip is placed in the stab wound. The patient is sent back to bed, care being taken that she stays in the prone position for 12 to 24 hours to prevent shoulder pain. There is no distress from inflation of the abdominal cavity or from any small amount of air that may be left after the procedure unless the patient assumes the upright position, in which event she will probably have shoulder pain from irritation of the diaphragm by the air. After 24 hours any air that has been left in the abdominal cavity will have been absorbed. If on the first attempt at visualization a frank hemoperitoneum is seen, the diagnosis is self-evident. While hemoperitoneum is not always due to a ruptured tubal pregnancy, it definitely justifies the institution of operative treatment.

Advanced Ectopic Pregnancy. In presenting a case of ectopic pregnancy that went 49 weeks before operation was performed, Roques and Winterton[9] review the literature on the subject and comment on the difficulty in diagnosis in such cases. After diagnosis has been made they believe that operation should be done as soon as possible and not delayed with the idea of obtaining a viable child. At operation, the important factor is the disposition of the placenta. They do not favor marsupialization with its long convalescence and resulting incisional hernia. If the placenta is found attached to the uterus or omentum, it should be removed, taking the uterus or omentum with it if hemorrhage is severe. If, however, the placenta is attached to intestines, they believe it is better to leave it *in situ* and close the abdomen without drainage. The placenta will be gradually absorbed over a period of about 12 months.

In reporting a series of 10 cases of *secondary abdominal pregnancy*, Reel and Lewis[8] state that the consensus at the present time is that most, if not all, abdominal pregnancies are secondary to tubal gestation. The mechanism by which the abdominal implantation takes place may be tubal rupture or tubal abortion. Before such a case can be considered as a primary abdominal pregnancy, the tubes, ovaries and broad ligaments must be demonstrated as normal; there must be no evidence of penetration of the broad ligaments by the fimbriated ends of the tubes and there must be no evidence of interligamentary rupture of the tubes. In this series which they report, all admittedly secondary pregnancies, there was not always a history of a missed period before the onset of illness but pain was universally present. Constipation which increased gradually from the onset of the present illness was the outstanding gastro-intestinal complaint. Bleeding occurred in 6 cases and was usually preceded or accompanied by cramp-like pains. The diagnosis of secondary abdominal pregnancy rests upon the history plus findings indicative of pregnancy such as softening of the cervix, bluish discoloration of the cervix, breast changes and so forth, and the presence of a pelvic mass. In handling such cases, if there is no sudden intraäbdominal catastrophe, the patient should be put to bed for rest, and a complete check of her blood, urine and general condition should be made. Transfusion before, during or after operation should be decided upon, depending upon the grade of anemia present and the urgency of operation. The surgeon must decide as to the most favorable time for operation, whether at the time the diagnosis is made, when labor begins or when fetal death occurs, remembering that at the latter time the placental blood supply is diminished with consequent lessened danger of hemorrhage. In regard to the method of handling of the placenta, they used marsupialization almost exclusively since they believe that drainage is a safeguard. Even though the removal of the gauze is rather painful, the pressure of the gauze pack is sufficient to control most of the bleeding and acts as an indicator of any especially active hemorrhage and affords drainage of any infection present. In removing the drain, they begin the first postoperative day and remove it fractionally in six days.

Hysterography has been employed by Greenhill[3] as an aid in the diagnosis of abdominal pregnancy. While such gestations are not often encountered and even when present are frequently not suspected, he believes that when such a diagnosis seems to be correct, injection of iodized oil into the uterus is not only a simple and relatively harmless procedure but presents absolute evidence of the presence of a pregnancy outside of the uterine cavity. A roentgenogram taken of an abdominal pregnancy taken without previous injection of an opaque substance into the uterus frequently shows a dead or live fetus in an abnormal location, but it does not prove that the fetus is outside of the uterus. Likewise in cases in which the fetus is dead and repeated attempts to induce labor by medicinal and mechanical means fail to bring about expulsion of the child, it is advisable to perform hysterography and occasionally one may be surprised to find an abdominal gestation. If the child is alive it might be dangerous to inject solutions into the uterus. In the case of abdominal pregnancy which he reports he believes that it was an ovarian pregnancy for the reasons enumerated below: 1, The uterus was entirely normal both on the Roentgen ray plates and at the time of operation. There were no scars on it and the only adhesions on it were from the fetal sac and these were slight; 2, both tubes were intact for their entire length; 3, both broad ligaments were entirely normal; 4, a careful search at the time of operation failed to reveal the right ovary; 5, the pregnancy mass was almost entirely free from adhesions. In advanced tubal gestations there are usually many adhesions and the placental attachment is often an extensive one; 6, the right tube coursed over and in front of the fetal sac as is usual in most ovarian enlargements; 7, microscopically, there was a layer of cellular tissue that resembled ovarian cortex and adjoining it was definite chorionic tissue.

Newer Aids in Treatment. Reporting from Knaus' Clinic in Prague, Hajek[4] extols the great value of *autotransfusion* in cases of ectopic pregnancy with severe internal hemorrhage. They have used the apparatus devised by Knaus, which is quite simple, in 22 cases giving blood in amounts varying from 250 to 1700 cc. The advantages of autotransfusion are the saving of valuable time by not having to type donors or test for cross-agglutination, the possibility of giving the patient large amounts of her own blood and the impossibility of transmitting any disease from donor to recipient. One of the point which is usually emphasized in this procedure is the addition of some solution such as saline or citrate to prevent clotting of the blood after it has been removed from the abdomen. Hajek states that such a procedure is harmful and unnecessary, since it reduces the vitality of the blood cells and, moreover, the blood removed from the abdomen following an ectopic pregnancy will not clot. Of course large clots are usually found in the abdomen in these cases, but the point which he makes is that the blood which remains as liquid blood in the abdomen will not clot after it has been removed. This fact is not generally known but he is absolutely sure of this fact and has kept such blood for a week without any evidence of clotting. The Reviewer, after reading this article kept some blood from a case of ruptured ectopic gestation for several weeks and it remained entirely liquid throughout that period, so his personal experience corroborates the statement of Hajek. Why such blood does not clot is not certain, but it is believed that it has been defibrinated by the intestinal movements. If fresh blood is added to it, clotting will occur and this should be remembered because if non-citrated blood from the abdominal cavity is being transfused, it should not be mixed with donor blood. The fibrinogen content of blood from the abdomen varies from 0.018 to 0.09% as against a content of 0.2 to 0.4% for normal blood.

Spinal anesthesia is considered by Koster and Sheinfeld[6] to be an important factor in minimizing the trauma of the operative procedure in a woman already damaged by a severe intraäbdominal hemorrhage. Maximal relaxation is afforded which insures easy, speedy operating with minimal tissue trauma. The fear that many of these patients already having a low blood pressure are not fit for spinal anesthesia because of its depressing effect on pressure, is entirely unwarranted in their opinion. The Trendelenburg posture insures sufficient gravity drainage back to the heart to prevent its contraction on empty chambers, no matter how complete the peripheral and splanchnic dilatation of vessels may be. Although there were only 2 cases in their series in which no blood-pressure reading could be obtained they have operated upon 12 other cases for various types of internal hemorrhage in which blood pressures were so low that a reading was unobtainable. These experiences in extreme cases, besides a familiarity with the uselessness of blood-pressure readings as a criterion of a patient's condition during operation under spinal anesthesia gained in over 10,000 laparotomies, convinces them that ectopic pregnancy is not only no contraindication to the use of this type of anesthesia but that it is a very satisfactory method to use in such cases. In spite of their enthusiasm it will probably be some time before the large majority of gynecologists will accept this as the method of choice since open-drop ether, with its stimulating action, has proved to be so satisfactory in such cases.

Fertility After Ectopic Pregnancy. Since an ectopic pregnancy may recur on the opposite side, Strassmann[11] investigated the question as to whether it was worth while to save the other tube at the time of operation. Of a series of 142 patients, there were 42 who were sterile or could not for various reasons be expected to become pregnant after operation. In the remaining 100 cases subsequent pregnancy was at least theoretically possible and of these he was able to find the subsequent history in 84 cases. Of this number, 31 (36.9%) became pregnant later, 28 (33.3%) having intrauterine pregnancies and 3 (3.6%) having a recurrent extrauterine pregnancy. Forty-seven intrauterine pregnancies occurred in these 28 patients and 32 of these resulted in full-time deliveries with 29 living children; there were 3 stillbirths. The mother of 2 of the still-born babies had syphilis. In this group of intrauterine pregnancies there were 4 premature deliveries, 10 miscarriages and 1 hydatidiform mole. There were some patients whose other tube was more or less affected and without an insufflation test it is almost impossible to tell whether the remaining tube is patent or not. Therefore there were undoubtedly some patients in this group who are practically sterile because of changes in the remaining tube. On the other hand, there may be a considerable number of patients in this group with a patent tube who did not desire to become pregnant again and who used contraceptive methods to prevent it. Concerning the surgical procedure employed, usually only the pregnant tube was removed and both ovaries were left. If one ovary has to be removed together with the tube, the chances for subsequent pregnancy do not seem to be much less, at least not 50% less. Of the 32 full-time pregnancies, 21 occurred in 14 patients with both ovaries left, while 11 occurred in 7 patients with only one ovary left. There is widespread opinion among laymen, and even among some physicians that the right ovary delivers only one sort of ovum (only male or female) and the left ovary the opposite. That this is not true was evidenced by the fact that there were 3 boys and 1 girl in cases in which the right ovary was preserved and 3 boys and 2 girls in cases in which the left ovary was preserved. One patient who had her left ovary removed had a boy and a girl later, both ova having come from the right ovary. It seems that tubal pregnancies occur more frequently on the right side, according to various statistics. An explanation which is not mentioned in the literature, based on an observation which Strassmann has made is as follows: A larger percentage of people are accustomed to sleeping on the right side than on the left, probably because lying on the left side sometimes causes uneasiness because of pressure on the heart. In many cases the ovum, after the bursting of the follicle, moves freely and passively in the abdominal cavity; therefore, since it would follow the law of gravity, it would appear that it might more often drop to the right side on which most people sleep. This explanation is, of course, purely speculative but it is interesting. The conclusions drawn from this report are that since the probability of intrauterine pregnancy after one ectopic pregnancy is about 10 times greater than the probability of another ectopic pregnancy, conservative surgery is advisable in order to preserve fertility. Only if the other tube is severely diseased should it be removed. In this connection it is well to remember, at the time of operation, that the non-pregnant tube undergoes certain acute changes in more than 50% of tubal pregnancies, such as swelling, redness and peritoneal friction, produced by hematomas. Such changes do not indicate removal of the tube as they usually disappear and do not interfere with subsequent fertility.

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DERMATOLOGY AND SYPHILOLOGY.

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CARBOHYDRATE AND WATER METABOLISM AND THE VITAMINS IN SKIN INFLAMMATION (DERMATITIS)

It has become increasingly apparent as knowledge of the chemistry of cutaneous processes has developed that cutaneous inflammation, and particularly inflammation due to infection, is greatly influenced if not actually conditioned by fundamental metabolic processes, including those involving carbohydrate, and water balance. In this review, an effort is made to collect the recent general and specific contributions on these two factors, and to add to them certain comment on vitamin functions wherever recent knowledge tends to suggest that they affect cutaneous inflammatory processes.

The Influence of the Carbohydrate. Oldest in point of time are certain contributions by Kendall[31a,b,32] and his associates pointing towards an influence of orally ingested carbohydrate upon vasomotor instability mechanisms which are clinically important predisposing factors to a wide variety of inflammatory reactions. Before proceeding to discuss the rôle of intestinal carbohydrate dyspepsia in skin inflammatory reactivity, a fundamental distinction should be drawn between the action of carbohydrate introduced *per os* and carbohydrate introduced parenterally and particularly into the blood stream. An investigation of this distinction as reflected in skin infections, was first conducted by Pillsbury and associates. Pillsbury and Kulchar,[55] after developing strains of staphylococcus which produced a "standard" or constant necrotizing ulcer in rabbits, succeeded in showing that the *parenteral* administration of glucose in 7.5 gm. doses per kilo every 12 hours had no effect on experimental staphylococcic skin infection, or seemed even to favor their healing. But when the dose of glucose was increased to 15 gm. per kilo in 24 hours and given at intervals of 4 hours, a very marked increase in the extent and severity of the experimental skin infection took place. This, however, likewise followed intraperitoneal injection of sodium chloride solution of the same tonicity as the sugar and in similar amount. This was the first intimation in their work that the influence of carbohydrate on skin infections is at least as much a function of its effect on water balance as on the glucose content of tissues. The findings of Craven[12] on the arsphenamine tolerance of dogs, which on a carbohydrate diet is impaired by the development of a hepatitis, led one of us (JHS[63]) to suggest that at least part of the effect of ingested carbohydrate on skin inflammation can conceivably be by way of its influence on the bacterial content of the intestinal tract with associated toxic liver injury. To this belief the further work of Pillsbury and Sternberg[56a,b] on skin infection in dogs afforded material support. They found that the course of experimental skin infections is more severe on a high carbohydrate diet than on a high fat diet, or fasting. They noted foul stools and diarrhea in the carbohydrate-fed animals. At this point theorization was reënforced as previously intimated, by the observations of Kendall who, in 1926, described a clinical syndrome of "intestinal carbohydrate dyspepsia" in man, with subsequent important observations on its bacteriology. It is this syndrome or an approximation to it which supplies a part of the vascular background for certain tendencies to skin inflammations.

Its close resemblance to the constitutional symptomatology of the rosacea complex in cutaneous disease, for example, the basis of acne rosacea, a pyogenic infection on a vasodilational base, was discussed by Stokes and Beerman.[64] The explanation drawn by them from the Kendall syndrome is as follows: A high carbohydrate intake in the presence of *Welch bacillus* and *B. mucosus capsulatus* in an intestinal content of low pH, favors the formation of histamine-like substances, whose toxicology as described, for example, by Cushny,[14] quite strikingly reproduces both the cutaneous vasomotor and general constitutional aspects of the rosacea complex. It would appear that the work of Kendall and his associates makes it possible to link the ingestion of carbohydrate in susceptible subjects with a histamine body absorption mechanism to provide a vasomotor and particularly vasodilational background for the localization and development of inflammatory processes on the skin. Since Kendall's work, Althausen, Gunnison, Marshall, and Shipmann[1] have conducted investigations tending to confirm both the clinical syndrome and the bacteriologic characteristics of "intestinal carbohydrate intolerance." They specifically name the development of vasomotor instability as a characteristic feature, and the other enumerated symptomatic details are identical with the findings both of Kendall as to intestinal carbohydrate intolerance, and of Stokes and Beerman on the constitutional background of the rosacea complex. Owles[50] states that inadequate pancreatic function and lack of intestinal diastase are not responsible for the symptomatology, and that the changed motility of the small intestine is probably by exclusion one of the most important factors.

So much, then, for carbohydrate by mouth. The next group of effects which carbohydrate may have on the course of inflammation concerns its influence on the hydration of tissue. Pediatricians, as Földes[21] points out, have clearly recognized the influence of high carbohydrate intake on water retention as the direct opposite of that of the protein-rich diet. Bischoff and Voit,[4] Moraczewski,[47] and Meyer-Bisch[44] have shown that in adults on a diet rich in carbohydrate, retention of both water and minerals develops. A recent summary by Hoelzel[28] points out the relation of carbohydrate restriction to resistance to colds, and cites the pertinent literature. Atchley, Peters and Kydd (*cf.* Cantarow[5]) have identified the effect of carbohydrate restriction as due to a pronounced loss of base (chiefly NaKCl). Since the sodium chloride of the skin is a leading element in its water retaining power, this explanation of the dehydrating effect of loss of carbohydrate seems particularly applicable to skin conditions. Földes, quoting Schiff,[59] points out that in experimental animals in which dehydration has been produced by a dry diet, no inflammatory reaction follows artificial infection, and although the animals die, this occurs without any such pathologic-morphologic changes in the organs as are common after infections under ordinary conditions. It is noteworthy that dehydration leading to an entire absence of inflammatory reaction can be produced if the dry diet consists mainly of proteins, but not otherwise. On a high carbohydrate diet, even if it is dry, sufficient water is apparently retained to prevent extreme dehydration. Schiff makes it quite clear that the usual signs of inflammatory reaction to infection are the ones which are absent if the water content of the tissues is inadequate, though intoxication and death from the infection may nonetheless take place. Thus inflammatory response to infection can, by way of tissue hydration, be markedly affected by carbohydrate intake.

Dealing with the skin as such, Tobler and Bessau,[72] and Klose[33] observed the special significance of the skin as a water depot in infants and small children as compared with adults, and pointed out the fact that exclusive carbohydrate nutrition produces marked retention of water in the skin.

The work of Pillsbury and Kulchar, previously referred to, approaching the subject directly in the experimental animal, took the first step towards elucidation of a variety of seemingly contradictory results. It has been pointed out on several occasions, notably by Tauber[69] in the treatment of furunculosis, and by Crawford and Swartz[13] in the treatment of acne, that a high carbohydrate intake *per os* and even the intravenous injection of moderate amounts of glucose stimulated recovery in pyogenic infections in man. When Pillsbury and Kulchar found in the rabbit that what might be called a large but not excessive dose of glucose intraperitoneally tended to promote rapid healing of skin infections in rabbits and that, when the dose became excessive, a marked increase in the extent of the skin infection occurred, their control gave them the clue to the explanation. The increased severity of the infection could not be ascribed to increased glucose as such, because the effect could be reduplicated by the administration of hypertonic sodium chloride intraperitoneally. They were, therefore, disposed to attribute the unfavorable influence of large amounts of parenterally introduced glucose on skin infections, to its effect on the water balance of the skin rather than its action as carbohydrate as a nutrient material for microorganisms. The unfavorable influence of glucose *per os*, a very different matter, is perhaps limited to those human beings or animals in whom a vasomotor instability factor is induced through varying grades of "intestinal carbohydrate dyspepsia" with their accompanying bacteriologic and intestinal absorptive effects.

A theory such as the foregoing is too simple for so complex a group of reaction possibilities. That the whole question of the rôle of carbohydrates in skin inflammation still lacks some essential clarifying linkage, was apparent from Pillsbury and Kulchar's inability to demonstrate a parallel in experimental animals between the glucose and water content of the skin. It is apparently not glucose as such which plays the unfavorable rôle in producing increased susceptibility of tissue to inflammation and infection.

Some indication as to this intermediate factor has been afforded by the very important work of Menkin[42a,b,43] and his associates. Pillsbury,[54] following the lead of Leake, Hall and Koehler, has pointed out the influence of *lactic acid* as a vasodilator, and rated it as important in the production of skin erythema. Menkin, through a series of extremely illuminating experiments on the production of pleural inflammation by turpentine injection, has apparently succeeded in showing that the lactic acid formed or present determines the characteristics of the inflammatory process at a site of irritation or infection (?), and that the formation of this lactic acid is a function of the disturbance of the local carbohydrate metabolism. This influence is at least in part exerted through the pH of the exudate in that a neutrophil response occurs in a neutral or slightly alkaline exudate, but that macrophages appear as the pH falls below 7.0, and the neutrophils previously present degenerate, producing pus.

It would thus appear that local inflammatory processes are profoundly influenced by the local carbohydrate metabolism insofar as it involves a free or abundant production of lactic acid from the locally available carbohydrate. It is this lactic acid production which determines to a considerable degree the pathologic characteristics of the locally excited inflammatory reaction.

To summarize, then, the influence of carbohydrate upon inflammations in the skin takes apparently a three-fold direction. It may influence them through the gastro-intestinal tract, in which intestinal carbohydrate intolerance may produce a pathologic picture leading to vasomotor instability and localized vasodilation (*e. g.*, the face) on which infective processes easily take root. It may, and does profoundly influence infective processes in the skin through hydration, for a high carbohydrate intake leads to water retention in tissue; and carbohydrate restriction leads to dehydration with corresponding disappearance of at least the inflammatory manifestations accompanying infection. Thirdly, the carbohydrate content of tissue influences inflammatory processes through the formation of lactic acid as a sequel of local inflammatory pathologic change, and with this formation of lactic acid marked change in the cellular and protective leukocytic reaction, incident on the change in pH, occurs.

The as yet unexplained favorable effect of intravenously administered glucose on local skin infections in man and animals remains a distinct gap in our equipment for interpreting the rôle of carbohydrate in cutaneous inflammation. It is conceivable that its favorable influence in moderate amounts is effected through assistance rendered the liver in dealing with circulating intoxicative agents and in the production of antibodies. It should be pointed out also that if markedly hypertonic solutions of glucose are, as is customary, employed (20 to 50%), the intravenous administration of the glucose itself will be an effective dehydrating agent. It is not even necessary that the glucose be markedly hypertonic, for as it is eliminated rather than utilized it will carry fixed base with it, leading to a loss of water by the tissues, including the skin, and hence a more favorable reaction in local inflammations.

There remains to be collected a group of less easily classified observations on carbohydrate factors in skin inflammatory processes. It has been noted by Ferannini[18] that the injection of parathyroid hormone is followed by a reduction ranging from 13 to 56% in blood sugar and an increase in carbohydrate tolerance in normal and diabetic subjects. Pillsbury and Sternberg[505] have pointed out the very favorable effect on lichen urticatus secured by the use of parathyroid extract administered intramuscularly. They explain the good effect as one largely upon calcium metabolism, but in view of this observation of Feramini's, it is conceivable that the action of the parathyroid extract is by way of a reduction of blood sugar and a carbohydrate depletion of tissues rather than through the calcium metabolism. Cantarow, Brundage and Housel[6] have, moreover, shown that the intravenous injection of calcium gluconate and calcium levulinate, the former often used in urticarial and skin inflammatory conditions, likewise is followed by a decrease in blood sugar from 10 to 31 mg. per 100 cc. within 5 to 15 minutes. It would appear thus that a variety of agents, including parathormone and calcium salts (and perhaps even the act of intravenous injection itself?) may lead to changes in the blood sugar and consequently of its mobilization in tissue with influence on the water content, and behavior under inflammation-inducing circumstances.

That carbohydrate intake influences fat secretion by the skin and hence the seborrheic group of dermatoses is supported by the work of Rosenfeld, Kuznitsky and Birk. Rosenfeld,[58] by extracting the daily output of sebaceous secretion absorbed by clean woolen underwear, showed that a diet rich in carbohydrate produces more oily secretion than one rich in fat. This was confirmed by the work of Kuznitsky[37] and Birk.[3] It is interesting in this connection that Wile, Eckstein and Curtis[76] noted involution of xanthoma in a mild diabetic on a diet low in carbohydrate and relatively increased in fats, while the lipemia increased and the tumors became more numerous when sugar was increased in the diet.

The local excretion of carbohydrate in sweat has developed an as yet not completely evaluated significance for skin infections through the studies of Usher,[73] Usher and Rabinowitch[74] and of Cornbleet.[11a,c] Usher and Rabinowitch found that in patients with diminished sugar tolerance there was an increased excretion of dextrose in the sweat after intravenous injection of dextrose, but that it was due apparently simply to an increased volume of the sweat itself. Usher's work suggested that an increase in the sugar content of the sweat of diabetics led perhaps to more favorable conditions for the growth of bacteria and fungi. In studying the bactericidal properties of the skin, Cornbleet[11a] found that sugars produced a loss in the self-sterilizing powers of the skin because of fluctuations in the blood sugar level, and the retarded rate of return to the fasting level. This occurs in diabetics with a high blood sugar but may also occur in certain normal persons who thus become a prey to cutaneous infections. This loss in sterilizing power, according to Cornbleet, can be prevented by avoiding the ingestion of large quantities of carbohydrates at one time. In investigating reducing substances in the sweat in the yeast dermatoses, Cornbleet[11c] sweated patients in an electric light cabinet and found that the victims of yeast infections secreted smaller amounts of sweat than normal persons, thus producing an artefact of increased glucose concentration on their skins. While the occasion for the greater concentration of reducing substances in the sweat of persons with yeast infections is not known, Cornbleet regards the fact as undoubted, and attributes to this increased concentration of reducing substance at least a part of the increased susceptibility to fungus infection. Cornbleet found, moreover, a direct relation between the concentration of sugar in the sweat and that in the blood stream, and that administration of sugar by mouth had a definite effect on the content of reducing substances in the sweat. The group with yeast infections showed a somewhat greater change in the content of sweat reducing substances after the ingestion of 50 gm. of dextrose than did the control group. He was not, however, successful in influencing materially the concentration of sweat reducing substances by attempts to reduce the blood sugar level.

The vitamin problem is also entangled with carbohydrate metabolism through several suggestive researches. Robertson[57] in 1934 reviewed the general question of vitamins and resistance to infection. Eddy and Dalldorf[16] point out that Funk[23] first called attention to the more rapid production of polyneuritis in animals deprived of vitamin B if the diets were rich in carbohydrate, and Peters, Kydd and Eisenman[51] feel that there is little doubt that recorded observations are indicative of a specific effect of vitamin B_1 upon carbohydrate metabolism. This influence is in their opinion not due merely to the general nutritional disturbance which accompanies the avitaminotic diet. But as in all speculation regarding vitamins, it sometimes seems as if a vitamin stick could always be found with which to beat the symptomatic dog. Carbohydrate tolerance and the bacterial flora of the gastro-intestinal tract are both quite markedly influenced by bowel motility (see Owles above) which in its turn is materially influenced by one of the known physiologic actions of vitamin B_1. It may accordingly be conceivable that the suggested action of vitamin B_1, as such, upon carbohydrate metabolism consists as much in hurrying the stuff through the intestinal tract in a stimulated peristalsis as in influencing the postabsorption carbohydrate metabolism as such. It is known, moreover, that vitamin B_1 in some way influences susceptibility to intestinal infections, and it may be that this effect on the bacterial content of the intestinal tract is the essential point of the application of the B_1 influence in carbohydrate metabolism. Be that as it may, there is reason to believe that vitamin B_1 materially influences some of the systemic effects of carbohydrate, and for that reason it may be a factor in behavior of the inflamed skin.

The Influence of Water Metabolism. Much that has been said in relation to carbohydrate metabolism has anticipated the following brief discussion of recent knowledge of the influence of water metabolism on skin inflammation. Following through the theoretical possibilities raised by Pillsbury and Kulchar's experimental work with glucose and sodium chloride administered parenterally in rabbits, Kulchar and Alderson[36] studied directly the effects of dehydration in rabbits on experimentally induced infections in their skins. They found that the dehydration not only did not unfavorably influence even to the point of lethal exit, the course of an artificially induced infection in the rabbit's skin, but that many animals apparently checked their infections, or at least the inflammatory manifestations disappeared, as they were deprived of water. In the reverse direction, when water was restored, the inflammation once more took up its full and even exaggerated activity. This series of observations confirms for the skin the now quite well established concept previously summarized that inflammatory reaction in the skin is profoundly influenced by water content.

This conception, not always with rational appreciation of its mechanism, has markedly influenced certain types of dermatologic treatment in the past few years. The most obvious method of reducing hydration of skin tissues is to reduce the intake of the salt primarily responsible for the retention of water in the skin; namely, sodium chloride. The low salt diets, of which the Gerson-Hermannsdorfer-Sauerbruch diet is the most conspicuous example, probably have other modes of operation besides their dehydrating effect. Nonetheless, their inflammation-reducing properties are so striking and their applicability so definitely extending beyond the original field of tuberculosis treatment, that the common factor of their dehydrating effect seems the best all-around explanation of their usefulness. Gerson's[21] insistence on the predisposition to inflammation and particularly to infective inflammation, which he rates as characteristic of the allergically predisposed individual, may be related to the acid base equilibrium and thus to the water balance of the involved tissues. It is thus possible to explain the clinical usefulness of low salt diets and diets swinging sharply towards the acid-ash side, in the treatment of a variety of eczematous inflammatory processes (Zitzke and Peters[77]). Just as a sharp reduction in carbohydrate intake will dehydrate, so a marked increase of protein intake (essentially an acid-ash diet calculated to remove chlorine and potassium ions from tissue) will act as an effective dehydrator through the induced diuresis. The acid-ash and high protein as well as the low carbohydrate diets may then be regarded as effective instruments for skin dehydration and their reported favorable action on eczemas explained to some extent in this way.

It is further interesting that salt and water, as Johnston and Maroney[30] have pointed out, have an important relation to the carbohydrate metabolism previously discussed, in that they are important factors in the oxidation of dextrose. These investigators point out, for example, that blood sugar rises after the administration of acid, and remains normal or diminishes after the administration of alkali. Their probably most suggestive generalization is that optimal oxidation of dextrose may be thought of as taking place slightly on the acid side of neutrality, and slightly on the concentrated side of normal as far as hydration goes. Applying this conception to the previously cited observations of Menkin on the importance of local pH due to lactic acid in inflammatory manifestations, it is conceivable that when optimal pH and concentration is maintained in the blood stream or body tissues at large, the general bodily utilization of available dextrose will reach its highest point and its storage in tissue will perhaps be reduced to a minimum. Accordingly, in theory, "idle" glucose, so to speak, should not on an acid trend and moderate tissue dehydration be available in the skin for the lactic acid rôle in inflammatory manifestations described by Menkin.

An important group of acidosis or "acid trend" inducing agents (*using acidosis* in a therapeutic sense, so to speak) are such acids as hydrochloric acid and such readily dissociable salts as ammonium chloride. To the administration of dilute hydrochloric acid by mouth is quasi-empirically ascribed the correction of gastric secretory deficiency and intestinal pH abnormality which influences the allergic and the intestinal carbohydrate intolerance phenomena in cutaneous disease. On the other hand, there is every reason to suppose from the existing experimental background that liberal doses of hydrochloric acid perform an important part of their function by dehydrating the patient and thus reducing the inflammatory reactivity of his skin. It is rather interesting, therefore, that fruit taken in large quantities, though classed as alkaline-ash food, has likewise a dehydrating effect. This effect of fruit develops from the elimination of carbonates formed in the breakdown of organic acids which combine with the alkaline constituents including metallic ions other than sodium which are present in the blood, tissues, and in the fruit juices themselves.

An interesting collateral of the water balance influence on cutaneous infections concerns cyclical menstrual exacerbations of such conditions as acne. The observation that immediately preceding menstruation women accumulate water in their tissues, is supported by numerous authors (Thomas,[70] Sweeney,[67] Molnar and Gruber,[46] Atkinson and Ivy,[2] Eufinger and Spiegler,[17] Okey and Stewart,[49] and Thorn, Nelson, and Thorn[71]). These authors have shown that a generalized edema regularly occurs in association with menstruation. In about one-third of the cases studied by some of these authors, there was an increase in weight and a swelling of the hands and feet at or about the time of menstruation. In most cases a rapid reduction occurred during menstruation. This corresponds to the time when the highest concentrations of estrogenic substance occur in the urine (Smith and Smith[61]) 12 days preceding menstruation (at or about the time of ovulation and the premenstrual period). Krohn and Zuckerman,[34] in studying water metabolism and the menstrual cycle in monkeys, found that the amount of water retained by the animal during the phase of swelling agreed closely with the observed increase in body weight. Heilig,[25] and Petersen and Milles[52] noted evidence of retention or delayed elimination of water and salts in the premenstrual period as compared with the intermenstrual period. Various explanations have been given for this delay in water excretion. Földes, recalling that Hasselbach and Bokelman and Rother noted an accumulation of acid substances in the body during pregnancy and the premenstrual period, believes that this accumulation may account for the water retention. In the latest work on this subject, Thorn, Nelson and Thorn (February, 1938) confirm this retention of water, sodium and chloride in human subjects during the intermenstrual as well as during the premenstrual period. They also were able to induce this retention in dogs by the injection of crystalline preparations of estrone, progesterone, pregnanediol and testosterone. In humans, the "onset of menstruation was associated with an increased renal excretion of sodium, chloride and water. Normal subjects, in whom no dietary restrictions were imposed, were observed to gain weight during the intermenstrual as well as during the premenstrual phase of the cycle. An increase in appetite and thirst was a striking symptom noted during the premenstrual period. The increase in the secretion of sex hormones and the increase in appetite and thirst appear," according to these authors, "to be contributing factors in body weight gain, which occurs during the menstrual cycle." It is quite possible that the effect of this retained water on inflammatory manifestations in the skin is the explanation of the monthly relapse annoyance in acne and acneiform eruptions.

The Influence of Vitamins. Whoever ventures to talk vitamin factors in cutaneous disease enters upon a territory in which confusion borderlines, cross effects and absence of adequate controls are as conspicuous as in the field of the clinical effects of endocrine preparations. The individual letter-denominated vitamins are in many cases complexes whose individual elements have more than one physiologic action. Until, therefore, the individual primitive extracted vitamin substances are replaced by synthetics which can be made the subject of adequate study in man as well as in the laboratory, confusion and uncertainty of statement must be the rule. Distinction must, moreover, be drawn, in all discussion of vitamin therapy, between the effects of deficiency of so-called normal vitamin intake, whose definition appears to vary with each discussor, and often fails of definition entirely; and the effect of hypervitaminosis or the therapeutic administration of amounts far in excess of the ordinary dietary content.

When these considerations are kept in mind one is reduced to a discussion of vitamin A, vitamin C and certain components of the B complex insofar as effect on cutaneous inflammation and infection are concerned. No form of skin inflammation appears to be directly attributable to lack of vitamin A. Avitaminosis A in man, as studied by Frazier and Hu,[22] Loewenthal,[39] Pillat,[53] and Nichols,[48] is responsible however, for a follicular keratodermia or keratosis with dryness and scaling of the skin which apparently reduces its resistance to microorganisms present on the surface, and predisposes particularly to pyogenic infections.

Swift[68] maintains that vitamin A is essential to the normal keratization of the muco-cutaneous surfaces, and that deficiency leads to the development of kraurosis vulvæ and leukoplakia, and to the pruritus associated with them. He blames the hypochlorhydria of the elderly women in whom these conditions occur, for their failure to absorb vitamin A even from diets which are adequate in this respect. It is interesting to note here how many actions might be attributed to such a procedure as the administration of hydrochloric acid by mouth. It could influence the local infection situation with secondary pruritus through dehydration and through acidification of the urine with a change in pH of the involved mucous surfaces. Yet it is credited with its good effect through the absorption of vitamin A. Simpson and Mason,[60] in 30 cases of senile vaginitis, both in elderly and castrated women, found that the administration of vitamin A in the form of halibut liver oil and cod-liver oil resulted in restoration of the vaginal epithelium to normal. Kulchar,[35] who has recently reviewed the literature on vitamin A deficiency in relation to infection, cites Findlay's observation[19] that avitaminosis A leads to a reduction in lysozyme in the tear secretion of rats sufficient to permit the growth of staphylococci and the establishment of infections about the eyes. Hill and White,[27] and Fleming[20] have demonstrated similar ferment-like substances in the skin, whose dependence on vitamin A deficiency has not, however, been studied. From this angle one finds another conceivable explanation of the apparent increase in pyogenic infections in individuals suffering from vitamin A deficiency. Additional suggestive evidence on the definite increase in resistance of the skin of infants receiving adequate amounts of vitamin A has been accumulated by MacKay[40] and by Clausen.[9a,b] That avitaminosis A, as such, is responsible for increased susceptibility to pyogenic infection in rats, was negated by the work of Sternberg and Pillsbury,[62] who found that this particular avitaminosis had no influence upon the course of a standardized experimental pyogenic infection in these animals.

The possible influence of vitamin C on inflammations and infections has been anticipated from its known importance to capillary physiology; from certain observations such as those of Höjer[29] on the effect of scurvy on the course of tuberculosis in guinea pigs, particularly in the matter of scar formation; and from a number of observations, beginning with those of Heise and Martin[26] that there is a markedly reduced excretion of vitamin C in the urine of tuberculous individuals, from which it is inferred that a larger amount of it is fixed or utilized in the defense against the tuberculous process. Important influences on the course of diphtheria have also been observed. This general information on the subject is not paralleled by anything in the way of an adequate study of the influence of vitamin C on cutaneous infection. The one present striking example of the importance of vitamin C in skin inflammation is that of arsphenamine dermatitis, in which Sulzberger and Oser[66] and Mayer and Sulzberger[41] who preceded them, claim credit for the observation that large doses of vitamin C inhibit arsphenamine sensitization in guinea pigs. Chapman and Morrell[8] reported that guinea pigs on a diet high in vitamin C developed marked sensitization reactions to neoarsphenamine, while pigs on a low vitamin C diet developed a less marked sensitivity. Cormia[10] found that variations in the vitamin C content of the diet of guinea pigs ranging from 0.025 to 0.2 mg. cevitamic acid had little influence on the development of cutaneous arsphenamine hypersensitiveness, but that a low vitamin C diet increased the intensity of reactions to the initial dose of neoarsphenamine, and retarded their involution. Large doses of vitamin C given for one week before a second test injection had little sensitivity-inhibiting effect. Further experimental work by this author indicated that guinea pigs which were unsensitizable during a summer period, sustained in a considerable proportion later flare reactions to intracutaneously injected neoarsphenamine as evidence of sensitization produced by a low vitamin C diet. Cormia's series apparently showed that the vitamin C content of the summer diet is what provides protection against neoarsphenamine sensitization, and that it can be artificially produced by 2 weeks of vitamin C deficiency. Huge doses of cevitamic acid entirely prevented the sensitization of 22 guinea pigs to neoarsphenamine. Previous and subsequent observations by Dainow,[15] Vanthey,[75] and Landfisch[38] indicated that cevitamic acid is an effective desensitizer in a variety of allergic conditions and that it is particularly influential in preventing arsphenamine dermatitis. Landfisch, for example, treated 25 patients, to whom an arsphenamine preparation could not be given safely, with synthetic cevitamic acid in ampules in doses of 0.05 gm. dissolved in 10 cc. of water and in tablet form for oral administration. Of the 25 patients, 12 male and 13 female, the evidence of intolerance disappeared in 11 male and 9 female patients (80%). In 4 female patients (16%), slight symptoms of intolerance were observed, and 1 male patient (4%) remained intolerant.

Cornbleet[116] has also shown as likewise in the case of vitamin A that vitamin C has a pigment reducing effect on the skin which was first manifest in patients with Addison's disease, and is probably related to the presumed deficiency of vitamin C in the adrenal cortex of such patients. Cornbleet states that pigment and vitamin C occur together in the skin, and that the pigment is apparently the anchor that holds the vitamin C. If pigment is not present, vitamin C is not stored in the skin in demonstrable amounts. In this particular, the action of vitamin C is antagonistic to that of copper, which hastens the darkening and precipitation of di-oxy-phenyl-allanin by ultra-violet light.

The influence of vitamin D on cutaneous inflammation is as yet virtually unknown territory. Through its influence on the absorption of calcium from the intestinal tract, viosterol may conceivably influence the course of cutaneous inflammation and affect skin irritability. The only direct therapeutic effect which is sufficiently clear-cut to suggest a sound causal background is the reported action of very large doses of vitamin D on psoriasis. The favorable influence of sunlight on psoriasis has long been empirically known. Ceder and Zon,[7] recognizing a possible rational explanation in the formation of vitamin D in the skin by sunlight, proceeded to use the vitamin in treatment in place of the sunlight. While the results as yet lack confirmation, they are very suggestive. These investigators treated 15 cases of chronic widespread psoriasis by 300,000 to 400,000 units of vitamin D from irradiated ergosterol daily. Eleven of the 15 cases obtained complete involution in a maximum of 12 weeks; 2 obtained a partial benefit and 2 showed no benefit. Apparently in the hands of these authors massive doses of the preparations used appeared to be relatively safe when administered to adults.

There remain to be considered as vitamin factors in skin inflammations, the various components of the B complex. Vitamin B_1, through its action on intestinal motility and carbohydrate metabolism may, as previously discussed, conceivably influence cutaneous inflammation. The recently recognized presence in the B complex of an achlorhydria-inhibiting factor is of some importance to those who ascribe to hypo- and achlorhydria important relations to the intestinal carbohydrate tolerance syndrome and its cutaneous vascular expressions, including rosacea. Since the influence of the "P-P" fraction of vitamin B is no longer under dispute, it is not discussed here. A supposedly specific anti-dermatitic factor in the B complex has been variously designated as "B_6," "Factor Y" and "vitamin H." It appears to be an element separate from the "P-P" antipellagra fraction, and its deficiency is responsible for the appearance of dermatitis in rats, affecting first the paws and the tips of the ears and nose. Milbradt,[45] of Leipzig, describes three types of widely differing rat dermatosis produced by lack of this vitamin "H," the third type resembling seborrheic dermatitis. He considers that there are essential differences between the avitaminotic dermatitis of rats and seborrheic eczema in man. Thus far the therapeutic application of vitamin H to the treatment of human seborrheic dermatitis has proved disappointing.

Thus far it appears, then, that high vitamin therapy, insofar as it concerns cutaneous inflammatory disease, has a not too highly specific and in fact rather shotgun quality concerned mainly (and especially in the case of the B complex) with the effect of the vitamins on the general constitution and nutrition of patients. The two nearest approaches to a specific use are found for vitamin A in keratodermic disturbances and their associated pyogenic infections, and in senile vaginitis and pruritus vulvæ; and for vitamin C in allergic dermatitic disturbances of the skin, particularly the prevention of arsphenamine cutaneous sensitization.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 21, 1938

The Effect of Dead Optic Vesicle on Explanted Gastrular Ectoderm. C. D. VAN CLEAVE (Laboratory of Anatomy, University of Pennsylvania). The influence of dead optic vesicle upon explants of prospective ectoderm of early gastrulæ and of body ectoderm from late neurulæ of *Amblystoma punctatum* was studied in these experiments exclusively by the explantation method. An ether extract of dead optic vesicles induced neither lens nor other structures in explanted body ectoderm of neurulæ. No inductions were obtained in explants of body ectoderm of neurulæ containing one dead optic vesicle. Explanted fragments of prospective ectoderm differentiated as epidermis. Explants of prospective ectoderm containing 2 to 6 dead optic vesicles were killed by this amount of dead material. Of 41 explants of prospective ectoderm containing one dead optic vesicle 17 showed inductions of definite neural character after 7 days' cultivation. Pattern and organization were lacking in the induced masses; entodermal and mesodermal rudiments were not observed. In 3 such explants the induced structures resembled optic rudiments and lentoids connected with a brain mass. The tentative conclusion is drawn that the influence of the dead optic vesicle may be imposed on the indifferent ectoderm. The results of similar experiments of Lopashov and of Holtfreter are discussed.

The Effect of Prontosil and Related Compounds Upon the Chemotropism of Leukocytes. DALE REX COMAN (Laboratory of Pathology, University of Pennsylvania). The purpose of these experiments was to determine whether or not substances of the sulphanilamide group increase chemotropism of leukocytes and in this way exert their therapeutic action.

The chemotropic effects of prontosil, sulphanilamide and setazine were studied by noting the response *in vitro* to these substances by rabbit neutrophils. Prontosil-soluble was adsorbed on kaolin, carbon, and hemolytic streptococci respectively. Control preparations of kaolin, carbon and streptococci were also studied. Sulphanilamide and setazine were used in crystalline form. The paths of leukocytes were followed under the microscope, as they moved in relation to these substances. The measure of chemotropism adopted was the number of micra per minute the cells moved toward the test substance. Prontosil did not significantly alter the chemotropic response of the leukocytes. Sulphanilamide, in the concentration employed, resulted in a cessation of cell movement. Setazine caused only slight positive chemotropism.

From these experiments it is considered unlikely that the therapeutic effect of these compounds is due to increased chemotropism of leukocytes.

Sulphanilamide in Experimental Streptococcic Meningitis. PAUL E. ADOLPH and JOHN S. LOCKWOOD (Laboratory of Surgical Research, University of Pennsylvania). Streptococcic encephalo-meningitis was produced in white rats by introducing the organisms into a traumatized subarachnoid space through a trephine opening in the skull. A fragment of agar was left in contact with the meninges to serve as a propagating nidus. The disease in controls was characterized by rapid onset of signs of meningeal irritation, death invariably ensuing within about 48 hours. Animals given 150 mg. of sulphanilamide once daily for 5 days did not survive much longer than controls. Those given 75 mg. twice daily for 5 days showed marked increase in survival rate (57%), and at the same time failed to display characteristic clinical signs of meningitis. In this group, the average length of life of those dying was about 7 days. Eighty per cent of the controls had hemolytic streptococci in the heart blood postmortem, whereas only 11% of the treated group showed this evidence of invasive infection. Examination of histological material revealed that the outstanding difference between control and treated animals (either those dying or those sacrificed) was the absence of evidence of tissue invasion in the latter group. Seventy-four per cent of control rats showed large numbers of free cocci in meningeal exudates, whereas only 36% of treated animals showed many free cocci, and in half of these the organisms were confined to a localized abscess. Control animals did not live long enough to develop abscesses. Sixty-three per cent of control animals showed cocci invading the cortex and meninges in advance of cellular exudate, while none of treated animals evidenced such invasion. From these experiments one might conclude that the principal effect of sulphanilamide is prevention of invasion.

Conclusions. Sulphanilamide given by mouth is capable of inducing marked alteration in the clinical and pathological course of experimental streptococcic meningitis. The effect of the drug seems to be to minimize invasion of blood stream and tissues.

The Cardiac Arrhythmia, Characteristic Effect of Thiobarbiturates, as Influenced by Changes in Arterial Blood Pressure. CHARLES M. GRUBER, VICTOR G. HAURY and CHARLES M. GRUBER, JR. (Laboratory of Pharmacology, Jefferson Medical College). The effects of intravenous injections in anesthetic doses of pentothal sodium, sodium thiopentobarbital and thio-ethamyl were studied in 68 dogs. In these, cardiac arrythmia was produced in every animal, after either the first or the second injection. If, after the injection of the thio-barbiturates in anesthetic doses, the rhythm of the heart remained normal, or had returned to normal, the increased blood pressure due to inactivation of one carotid sinus (by occlusion of the common carotid) initiated the cardiac arrhythmia in 70% of the experiments. Cutting both vagi had no influence on the effect of carotid occlusion in producing this cardiac arrhythmia in animals under thio-barbiturate anesthesia.

Atropine sulphate, picrotoxin and metrazol injected intravenously did not affect the arrhythmia. Ouabain, tyramine and ephedrine, on the other hand, when injected into dogs under thio-barbiturate anesthesia, initiated cardiac arrhythmia in every instance. Intravenous epinephrine caused the arrhythmia to disappear. Acetylcholine when given intravenously caused the dipsapearance of the arrhythmia in all animals in which atropine sulphate was not previously injected. In those experiments in which atropine was injected, acetylcholine was ineffective.

Histamine acid phosphate, quinidine sulphate, amyl nitrite, and glyceryl trinitrate restored the regular rhythm to the heart. This we believe to be due to the decrease in blood pressure. Hemorrhage likewise will convert cardiac arrhythmias due to thio-barbiturates to a normal rhythm.

The Rôle of the Cervical Nerves in Facial Sensations. F. H. Lewy (Departments of Physiology and Surgery, University of Pennsylvania). The normal sensibility of the face was tested in normal persons and in patients with unilateral trigeminal neuralgia. In the latter, tests were also made on the pathological side both before and after subtotal section of the fifth nerve root. Frequency curves in which the threshold values of the touch points are plotted against the number of incidences of responses, show two maxima, the one at 15 volts, the other at 40 volts. After section of the fifth nerve root, the maximum at 15 volts disappears while the maximum at 40 volts remains unchanged. Frequency curves of the time factor of touch sensations show a similar two-peaked curve. The first of these two peaks disappears after section of the fifth nerve root. It is inferred from these observations that the touch points having a low mechanical and electrical threshold and a low time factor are innervated by the fifth nerve, those having high values are supplied by the cervical segments. The frequency curve of the time factor to painful stimuli has only one maximum. The majority if not all pain points within the area of the fifth nerve seem to be supplied by the fifth nerve only. The disturbance of pain sensibility after subtotal section of the fifth nerve is characterized by complete disappearance of some pain points—penalgesia. Those points that remain show a high threshold—hypalgesia.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
MAY, 1938

ORIGINAL ARTICLES.

PROBLEMS RELATING TO THE INVASIVE PROPERTIES OF HEMOLYTIC STREPTOCOCCI AND THEIR CONTROL BY SULPHANILAMIDE.*

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THE remarkable results that have been obtained recently in the treatment, by chemotherapy, of hemolytic streptococcal infections, form an incentive to study with renewed vigor many problems relating to the invasive properties of hemolytic streptococci, and to the resistance of the body against this organism.

The hemolytic streptococcus has peculiarities that distinguish it from other known bacteria. One of its striking attributes is its ability to cause infections of the most varied character. In the first place, it is well known that a small number of people harbor, from time to time, hemolytic streptococci in their fauces or tonsils. It has been estimated that during the winter months in New York and Baltimore 9% to 14% of normal individuals are temporary carriers of this organism.[6,40a,56,71] A few persons may persistently carry the organism in their fauces. When, however, the hemolytic streptococcus actually invades the body, it may give rise in some patients to a comparatively benign local infection of the skin, or a mild tonsillitis; in others, it may cause such specific diseases as scarlet fever or erysipelas; in a third, it may produce a fulminating general septicemia following an insignificant local lesion, or fatal meningitis complicating mastoiditis. It is particularly prone to invade tissues made susceptible by some comparatively benign disease such as measles or influenza, and may convert epidemics of these infections into veritable plagues.

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* The Sixteenth Nathan Lewis Hatfield Lecture of the College of Physicians of Philadelphia, March 2, 1938.

Most of the local infections, except, of course, those that involve the serous surfaces, are sometimes so mild as to be almost insignificant; but, on the other hand, any one of them may assume such a virulent character as to be fatal almost within a few hours.

The greatest dangers in any form of streptococcal infection come from a spread of the process locally, or an invasion of the blood stream. The character, form, severity, and outcome of the infection must depend upon the portal of entry, the virulence of the infecting organism, and the degree to which the patient is able to marshal together his forces of defense.

It is not necessary to dwell upon the variations in the form of the infection that depends upon the portal of entry of the organism for it is obvious that when hemolytic streptococci are introduced into the skin the clinical characteristics of the disease that follows are totally different from those resulting from contamination of the uterine canal or infection of the throat.

The infections in man are due principally, though not exclusively, to hemolytic streptococci belonging to the Lancefield Group A.[38b] Occasionally, members of other groups, notably the minute hemolytic streptococci of Long and Bliss,[4] which are included by Lancefield in Group F, cause infections in man, while anerobic hemolytic streptococci are frequently found in lung abscesses (Fisher[21]) and may cause puerperal sepsis.

Type specific strains of hemolytic streptococci are recognizable within Group A (Griffith,[30] Lancefield[38a]) and localized epidemics have been traced to a single specific type (Griffith,[30] Swift, Lancefield and Goodner).[65] The infections occurring in these epidemics are, however, of various forms, and up to the present time it has not been possible to demonstrate conclusively that scarlet fever and erysipelas, which represent highly differentiated forms of streptococcal infections, are caused regularly by a single specific strain of hemolytic streptococcus, though a limited number of Griffith's 20 types have been obtained from epidemics of scarlatina,[30] and by Pauli and Coburn[53] from infections of the throat preceding attacks of rheumatic fever. In this respect, the situation seems to be analogous to that which exists in lobar pneumonia or in epidemic meningitis.

Strains of hemolytic streptococci belonging to the Lancefield Group "A" produce substances some of which are certainly injurious to the host. Among these are the erythrotoxins, which are familiar as causing the skin reaction, the hemolysins, extensively studied by Todd,[68a,b] fibrinolysin described by Tillett and Garner,[67a,b] leukocidin and the toxic material extracted from hemolytic streptococci by Weld.[72] It is probable that the spreading factor of Duran-Reynolds,[18a,b] which may be derived from the bacteria themselves, a somewhat similar substance obtained by Vally Menkin[46] from inflammatory exudates, and the fibrinolytic property of the organism, are largely responsible for the advance of the infection through tissues.

Soluble antibodies to these noxious substances are formed by the host, but their importance in combating the infection during its early stages, and the part which they play in bringing about recovery is not entirely clear. The bactericidal property of the blood for hemolytic streptococci may be much increased during these infections. When the infection remains localized, however, the increase, according to Hare[32] may only be demonstrated during convalescence, or may not appear at all. If the infection becomes generalized, on the other hand, there is an early and marked increase in the bactericidal property of the blood, not only in those patients who recover, but in about half of those who succumb to the infection. Keefer, Ingelfinger, and Spink[36] have been able to confirm these observations. Hare believes he can show that the increased bactericidal property of the blood is due partly to a bacteriostatic or bactericidal property of the serum and partly to the formation of bacteriotropins which bring about an increase in the amount of phagocytosis, even though the leukocytes may actually have sustained some injury. In this particular, and perhaps highly important, protective mechanism, one must take into account the activities of the cells of the body as well as the property of the serum.

During one phase or another of the infection, specific agglutinins and precipitins; antihemolysin and antifibrinolysin as well as neutralizing substances to the erythrotoxin (scarlatina), may be demonstrated in the serum. And finally, following repeated infections by hemolytic streptococci, the skin of an individual may become highly sensitive to the nucleo-protein of the hemolytic streptococcus or to the products of its growth.

It is probable, therefore, that the variety, the special character, the severity, and the outcome of infections by hemolytic streptococci are determined by many factors. The disease will depend on the one hand upon the predominance of one or another of the biologic properties of the infecting organism and on the other upon the varying states of resistance or susceptibility, immunity, or allergy that modify the responses to infection in the host. It is the interaction of these forces that is responsible for the variegated clinical pictures in streptococcal infections, and that renders their course, to say the least, kaleidoscopic.

As examples, one may mention scarlet fever, in which the rash and early intoxication are presumably caused by circulating toxins while the complications, such as adenitis, meningitis, or arthritis are due to an invasion of the tissues by the bacteria themselves. After recovery, an immunity to the erythrotoxin protects against second attacks of scarlatina, but not against subsequent and often serious infections by hemolytic streptococci. Erysipelas, on the other hand, is characterized by a local spreading infection which endangers the life of the patient by invasion of tissues or by extension of hemolytic streptococci into the blood stream. Recovery is often followed by subsequent attacks. This susceptibility to repeated attacks of erysipelas has been attributed to the development of an allergic state towards hemolytic streptococci or to the products of their growth. Still further variations occur, for a slight infection of the skin may be followed almost immediately by a rapidly fatal septicemia, as another example, or a mild attack of pharyngitis or tonsillitis may be complicated by acute hemorrhagic nephritis with violent onset, or by an exacerbation of rheumatic fever.

When we search for criteria to measure the progress of streptococcal infections it is found that a continuous local spread of the infection and an invasion of the blood by hemolytic streptococci are two particularly unfavorable signs. We have been interested for some time in the latter problem and have analyzed 166 cases of hemolytic streptococcal septicemia gathered largely from the adult services at this hospital in order to gain information about the types of infection in which an invasion of the blood is most likely to occur and to learn what the ultimate outcome may be in these patients.*

It is well known that septicemia due to hemolytic streptococci results fatally in a large proportion of cases. Of the 166 cases that I have analyzed 125 died, a fatality rate of 75.3%. This corresponds almost exactly with the figure given by Keefer, Ingelfinger, and Spink,[36] who in a series of 246 patients found the mortality to be 72%. An invasion of the blood, however, is not of equally serious significance in all forms of infections. This is shown in the accompanying Table 1, where it may be seen that, excluding the few cases of scarlatina and endocarditis, the highest mortality rate (85.7%) occurred in erysipelas and cellulitis, and the lowest (53.5%) in mastoiditis. These figures are again very close to those published by Keefer and his associates. The number of cases of puerperal

TABLE 1.—MORTALITY IN DIFFERENT FORMS OF β HEMOLYTIC STREPTOCOCCAL INFECTIONS WITH BACTEREMIA.

	No.	Death.	Mortality, %.
Endocarditis	5	5	100.0
Scarlatina	3	3	100.0
Erysipelas and cellulitis	28	24	85.7
Abscesses and wound infections	43	35	81.4
Primary focus obscure	39	31	79.5
Tonsillitis and respiratory infection	15	9	60.0
Puerperal sepsis	5	3	60.0
Mastoiditis	28	15	53.6
Total	166	125	75.3

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* I am indebted to Drs. Dean Lewis, Samuel Crowe, and Nicholson Eastman for permission to include cases occurring on the surgical and obstetrical services.

sepsis is so small that our figures are probably not trustworthy. Colebrook and Purdie[13] give an average mortality rate of 71% for 82 cases, observed during 4 years from 1932 to 1935.

The mortality rate in all infections due to hemolytic streptococci will be influenced not only by the form of infection, but by the age of the patient, his previous physical condition, and the presence of such chronic diseases as diabetes. We need not enter into a discussion of these factors, however, since Keefer, Ingelfinger, and Spink have considered them in detail.

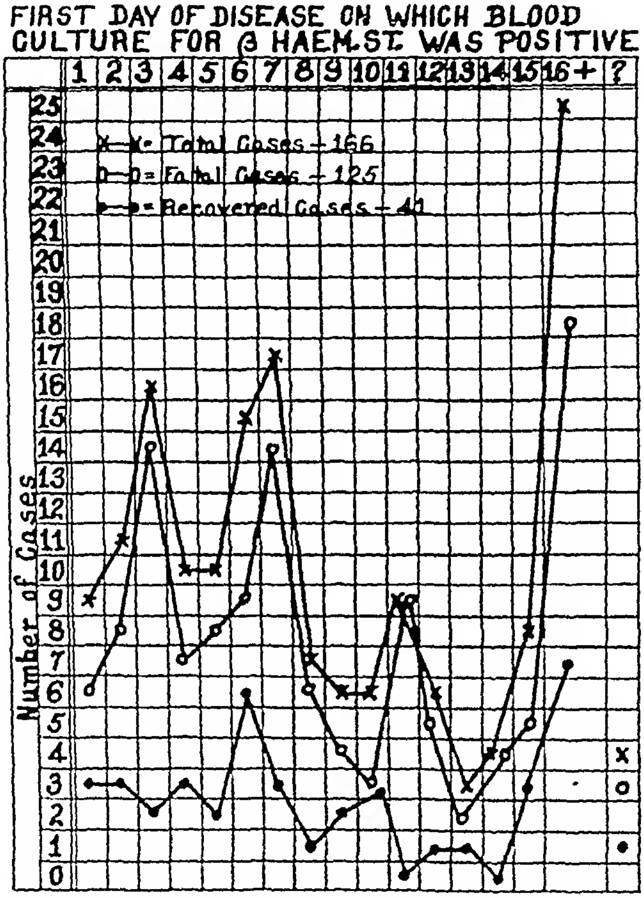

Chart 1.—Day of appearance of positive blood culture in streptococcemias.

We have been interested to gain some information concerning the day of disease upon which invasion of the blood first takes place. Although it would require daily blood cultures from the moment of onset of the infection to obtain accurate figures, still Chart 1 has some slight value, for repeated blood cultures were made on 2 to 10 occasions from 78 of the patients, 26 times in those that recovered, and 52 times in those that died, and in 24 patients positive cultures were preceded by negative cultures.

The chart shows two periods in which an invasion of the blood was most frequently demonstrated, first during the first week of the disease, 88 cases, and second after the fifteenth day of disease, 16 cases. The fatal cases appear to be almost entirely responsible for these peaks. The early deaths occurred in the patients with acute fulminating infections, the later deaths represent, in general, terminal invasions of the blood.

In the fatal cases, the number of colonies of hemolytic streptococci in the blood varied from less than one colony per cc. to myriads. In 3 instances the blood cultures became negative before death. In the non-fatal cases, the numbers of colonies per cc. varied from less than 1 colony per cc. to 125 colonies per cc. in 1 case of mastoiditis. In 7 other patients the number of colonies per cc. varied from 25 to 80 on at least one occasion. The septicemia in 4 of these 7 cases followed mastoiditis. In 10 of the 26 cases that recovered, more than 1 positive blood culture was obtained. In 1 case of mastoiditis 6 out of 10 cultures proved positive, and in 1 case of tonsillitis 4 out of 6 blood cultures showed a growth of hemolytic streptococci.

The duration of the disease in the 125 fatal cases was as a rule short, varying from 2 to 105 days, but averaged only 12.5 days (Table 2). In 103 (82.4%) of these cases the disease lasted less than 3 weeks, and in 42 (or over one-third) the patient died within 1 week after onset (Table 3). In the non-fatal cases, the disease was prolonged, frequently being complicated by metastatic foci of infection and sometimes by relapses with reinvasion of the blood. In 41 patients the average duration of disease was 45.5 days; the shortest period of illness being 4 days, the longest being 6½ months.

TABLE 2.—AVERAGE DURATION OF INFECTIONS IN DAYS.

	Recovered.		Fatal.		
	No.	Duration.	No.	Duration.	Total.
Scarlatina	..	...	3	12.5	3
Erysipelas and cellulitis	4	22.0	24	9.1	28
No primary focus	8	56.6	31	14.2	39
Abscess and postoperative	8	53.85	35	9.8	43
Respiratory infections	6	24.0	9	13.6	15
Puerperal sepsis	2	77.0	3	9.5	5
Mastoiditis	13	44.5	15	19.8	28
Total	41		120		161

TABLE 3.—DURATION OF DISEASE.

	Weeks.															
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	Total.
Recovered	3	3	6	1	3	6	5	1	2	2	3	1	2	1	1	40
Fatal	42	40	21	7	6	1	2	1	3	..	1	..	..	..	1	125

The cases of mastoiditis, otitis media, and sinusitis showed the greatest number and variety of complications, for they occurred in 30 (93.7%) of all 32 cases. The patients with erysipelas and cellulitis developed the smallest number of complications, for these occurred in only 13 (44.3%) of all 28 cases. It is well to recall the fact that the mortality was highest in the patients with erysipelas and cellulitis and lowest in those with mastoiditis.

Even more dangerous to the life of the patient than an invasion of the blood stream by hemolytic streptococci is an extension of the infection to the peritoneal cavity or to the meninges. Peritonitis occurs most commonly as a complication of puerperal sepsis, while meningitis is the dreaded sequel to mastoiditis and sinusitis.

Recovery from streptococcal peritonitis rarely occurs. All of Keefer's 7 cases died.

Recovery from streptococcal meningitis is perhaps still less common. Few proven cases of the disease, before the use of prontosil or sulphanilamide, are known to have survived. Gray[29] has stated that streptococcal meningitis is fatal in 97% of cases; Anderson[1] collected from the literature 66 cases that had recovered. Trachsler and his associates[69] have found 110 recoveries recorded, but state that only 2 of 71 cases that they had observed previous to the use of prontosil and sulphanilamide had survived the infection. Neal and Appelbaum[49] state that among 274 cases of streptococcal meningitis only 15 recovered, and but 9 of these were due to β hemolytic streptococci. From these figures, one would be justified in concluding that at the very most 5% to 10% of cases of meningitis due probably to all forms of streptococci recover, and that the mortality in β hemolytic streptococcal infections approaches or exceeds 95%.

Sulphanilamide. Now that we have established some standard by which we may estimate the value of any therapeutic measure employed for most serious forms of hemolytic streptococcal infection, namely those associated with septicemia, meningitis, and peritonitis, we may discuss the results that have been obtained by the most recent therapeutic procedures.

Among the numerous chemical compounds and soluble dyes that have been employed in an effort to find one that would prove to be effective against the hemolytic streptococcus, there is only a single group that deserves consideration, but this group warrants all of our attention.

For a year or two before Domagk's[17a,b] communication in 1935, a chemical called "Prontosil" or "Streptozon" had been used in Germany for the treatment of various infections. Levaditi and Vaisman[39] as well as Domagk were actively engaged at this time in studying the experimental effects of the drug in mice. But the original chemical substance, the hydrochloride of 4 sulphamido 2′, 4′ diamino 3—benzene, known as "prontosil," was soon replaced by the disodium salt of 4 sulphamido-phenyl-2′-azo-7′-acetyl amino-l′-hydrooxynapthalene-3′, 6′ disulphonic acid, a more readily soluble compound known as "Prontosil soluble." At about this time Tréfouël, Tréfouël, Nitti, and Bovet,[70] working in the laboratory Fourneau in Paris, showed that para-aminobenzene sulphonamide, now known as sulphanilamide, was highly effective in its curative action upon mice infected with hemolytic streptococci.

It would hardly be profitable to discuss in detail the chemical structure of these compounds, or to do more than allude to the fact that numerous allied substances are constantly being synthesized and tested, in the hope that a drug may be found which possesses advantages over sulphanilamide, or that is active against other bacteria. But one cannot leave this subject without at least mention of the chemical, sodium sulphanilyl sulphanilate, which Dochez[1c] has recently found to have a remarkably beneficial effect in distemper, a disease due not to bacteria but to a filterable virus.

We will, therefore, confine our attention to the properties of para-aminobenzene sulphonamide, or sulphanilamide, and consider exclusively its therapeutic effects upon infections due to hemolytic streptococci, even though it is now known to be of value in the treatment of infections due to meningococci and gonococci, to be curative in some instances of pneumococcus meningitis or in other infections due to pneumococcus Type III, and to modify, as Rich and Follis[57] have shown, the development of experimental tuberculosis in the guinea pig.

During 1935 many brief clinical reports appeared both in the German and French literature, indicating that the drug was of value in the treatment of streptococcal infections, but it was not until the careful clinical and experimental work of Buttle, Gray, and Stephenson[9] and of Colebrook, Buttle, and O'Meara[14] stimulated the work of Long and Bliss that the drug became at all familiar in this country.

The pharmacologic action of the chemical has been studied experimentally, particularly by Marshall, Emerson, and Cutting.[42,43a,b,44a,b] They find that it is absorbed quite as rapidly from the gastrointestinal tract as from the subcutaneous tissues, and since it is not highly soluble, oral administration is desirable when this is possible. It has been suggested by Long and Bliss[40b,c] that an average daily dose of 1 gm. by mouth per 20 pounds of body weight is theoretically desirable, but in practice, it is often useful to administer somewhat larger doses to adults for a few days. A daily dose of 6 to 9 gm. for 2 to 3 days may be advisable in exceptionally severe infections, and Colebrook and Purdie[13] have employed, under these circumstances, as much as 12 to 15 gm. a day. The optimum dose is usually best arrived at in the individual case by determining the blood concentration, which according to Long and Bliss should reach a level of approximately 10 mg. %. The drug may be given, however, by the subcutaneous route or intrathecally when this seems necessary. It is soluble in the proportions of 8 gm. to 1000 cc. of water. An accurate quantitative method for the determination of the chemical in solution has been described by Marshall and his associates,[43a] so that it is a comparatively simple matter to determine its concentration in the blood, urine, body fluids, and tissues. The chemical can be detected in the blood within an hour after it has been administered either orally or subcutaneously and within 3 or 4 hours reaches its maximum concentration in the serum. Within a few (3 to 4) hours after ingestion it appears in the urine and continues to be excreted for 24 to 48 hours. In the dog, the substance appears to be excreted unchanged in the urine; while in the rabbit, cat, and man, varying amounts of the chemical appear as an acetyl derivative, which is practically inactive therapeutically.[43b] The acetylated product forms a comparatively large proportion of the material that is excreted in the rabbit. The chemical is readily diffusible and is found in the spinal fluid and pleural exudates of man in concentrations only slightly lower than those in the blood. Indeed Marshall and his associates have found that it permeates most of the organs of the body, so that concentrations comparable to those in the blood can be found in the skeletal muscles, heart, skin, and viscera. The lowest figures were obtained for fat and bone. The diffusibility of the chemical appears to account for the fact that the sulphanilamide clearance in the dog amounts to only 20 to 30% of the creatinin clearance determined simultaneously. A large part of the sulphanilamide, presumably filtered through the glomeruli, is reabsorbed by the tubular epithelium. It was found by Marshall in some cases of nephritis that the excretion of the drug was considerably delayed and as this proves to be of fairly constant occurrence, equivalent doses of the drug result in higher concentration in the blood of nephritics than in patients with normal kidneys. It is important that the drug should be administered in sufficient quantities and at the proper intervals to maintain as constant and as nearly optimal concentration in the circulating blood as possible. As the drug is rapidly excreted in the urine, Marshall has suggested that the chemical be administered at least every 4 hours. When one follows this method it has been found that it requires from 2 to 3 days to establish an equilibrium between the amount ingested and the amount excreted, and thus to maintain the concentration of the drug in the blood at a level of at least 10 mg. %. This is the concentration which Long and Bliss[40b,c] have estimated to be desirable or even essential in order that the drug should be most effective.

It is, naturally, of the greatest importance that we should understand the manner in which the drug produces its effect. It is known that neither "Prontosil" nor "Prontosil soluble"[12] has the slightest injurious action upon hemolytic streptococci *in vitro*. It is now recognized, however, that these drugs probably owe their therapeutic action to the fact that they are converted into sulphanilamide in the body (Long and Bliss, Fuller).[25,40c] Unlike prontosil, sulphanilamide itself, as has been shown by Buttle,[9] Colebrook,[14] Long and Bliss,[40a] and Fischer,[20] exerts a definite and measurable effect upon the growth of hemolytic streptococci *in vitro*. This can best be demonstrated by employing cultures of hemolytic streptococci which contain very small numbers of organisms per cubic centimeter. Under these circumstances the chemical possesses a definite bacteriostatic effect, suppressing the multiplication of the bacteria. It does not, however, in the concentrations used, destroy the hemolytic streptococci, as subsequent growth is always observed.

Although one can probably determine the activity of sulphanilamide against any variety of bacteria by this procedure, a more satisfactory method is to measure the therapeutic properties of the drug against infections produced experimentally in animals.

Studies instituted to examine the mechanism by which sulphanilamide acts in the body indicate that it acquires no further virtue than that which can be demonstrated in the test tube. Levaditi and Vaisman[39] suggested that the chemical rendered hemolytic streptococci more susceptible to phagocytosis in the peritoneum of the mouse by injuring or destroying their capsules and neutralizing the leukocidin, but Bürgers[8] could not confirm the observation, and the work of Long and Bliss[40d] and of Gay and Clark,[26] seems to have established the fact that the drug simply retards the growth of hemolytic streptococci in the peritoneum of the mouse or in the pleural cavity of rabbits, and that it has *in vivo* no other demonstrable property than that which it possesses *in vitro*, namely one of bacteriostasis. Phagocytosis appears to be the only demonstrable means that the body has to dispense with the infecting organism. This is carried on in the mouse by the polymophonuclear leukocyte, though Domagk[17c] has shown that macrophages are also active during the early stages of the process. McKinney and Mellon[41] conclude from their experiments that the phagocytic response depends upon the type of organism, some strains calling forth neutrophils, others implicating the macrophages. That neutrophils, nevertheless, are essential to the protective mechanism of the mouse is definitely indicated by the experiments of Long and Bliss,[40d] who showed that treatment by sulphanilamide became completely ineffective in mice made leukopenic by injections of benzene. In the rabbit, according to Gay and Clark,[26] protection depends upon active phagocytosis by the macrocyte. It must be noted, on the other hand, that Mellon, Gross, and Cooper,[45] experimenting with strains of hemolytic streptococci of varying virulence, could not convince themselves that phagocytosis was responsible for the therapeutic effect of either sulphanilamide or of "prontosil" in infections of mice or of guinea pigs, while Osgood,[51] working with cultures of human marrow, concludes that the value of these drugs rests upon their ability to neutralize toxins.

Since it has been possible, through experimental and clinical studies to establish some of the conditions under which therapeutic action of sulphanilamide is most effective, we must conclude that there are at least two which are essential. The first is that the infecting organism should be subjected to a concentration of the chemical sufficient to produce an optimal bacteriostasis; and the second, that the body should acquire and retain the power to rid itself of comparatively small numbers of viable and perhaps highly virulent organisms. One method, by which this seems to be effected in experimental animals, is through phagocytosis.

The clinical results which have followed the use of sulphanilamide tend to bear out some of these assumptions, but the literature is literally flooded by reports of such short series of cases, and the drug is being employed so widely for such diverse and such indefinite types of infection, that it will require prolonged and critical study to determine not only the conditions in which it is undoubtedly of immense value, but to define in addition the limits of its usefulness, as well as to recognize the dangers incidental to its employment.

The drug seems to be effective in infections due to several, and possibly all, types of hemolytic streptococci belonging to the Lancefield Group A,[13] and in infections of animals caused by some but not all strains of Group C (Lancefield).[62] Long and Bliss[40f] have found the drug inactive in urinary infections due to hemolytic streptococci belonging to Group D (Lancefield), while Colebrook and Purdie[13] have not observed that it has any effect upon puerperal infections caused by anerobic streptococci.

There is not, at the present time, sufficiently accurate information at hand to discuss the action of sulphanilamide upon all forms of infection due to hemolytic streptococci, and I will, therefore, confine the discussion to a consideration of its therapeutic effects in a few of the more serious forms of streptococcal infection.

One of the severest tests to which the efficiency of this drug could be put is in the treatment of meningitis due to hemolytic streptococci, for as we have seen at least 90 to 95% of these patients die. The therapeutic results in this type of infection have been nothing short of brilliant. During the last few months recoveries have been reported in at least 39 patients who were treated with prontonsil or sulphanilamide or a combination of the two drugs. Undoubtedly the recoveries at the present time far exceed this number. Trachsler and his associates[69] have recorded 4 recoveries out of 7 cases, Long and Bliss[40b,c] 2 out of 4, Schwenke and his associates[61] 3 out of 4, and Neal and Appelbaum[49] 13 recoveries out of 17 cases.

Most of these recoveries have occurred in patients suffering from streptococcal meningitis secondary to mastoiditis, and it is important to pay some attention to the combination of circumstances under which the drug was often used. In a large proportion of cases the primary focus of infection was drained surgically; in many, the drug, in the comparatively high concentration of 0.8%, was brought in direct contact with the infected meninges by intrathecal injections, and in all the infected meninges have been drained repeatedly by lumbar puncture. It seems reasonable to suppose that these accessory procedures were of some benefit, for it cannot be sufficiently emphasized that, as far as we know at the present time, the actual cure of the infection and elimination of the hemolytic streptococcus depends in the last analysis, not upon the drug, but upon the protective forces of the body. These are brought to bear upon an invading organism, made particularly vulnerable in some way by the action of the drug. Colebrook and Purdie[13] have shown for instance, that the whole blood of patients suffering from streptococcal infections who have been treated with sulphanilamide becomes highly bactericidal for hemolytic streptococci, though it is known that the drug does not impair the virulence of viable organisms.

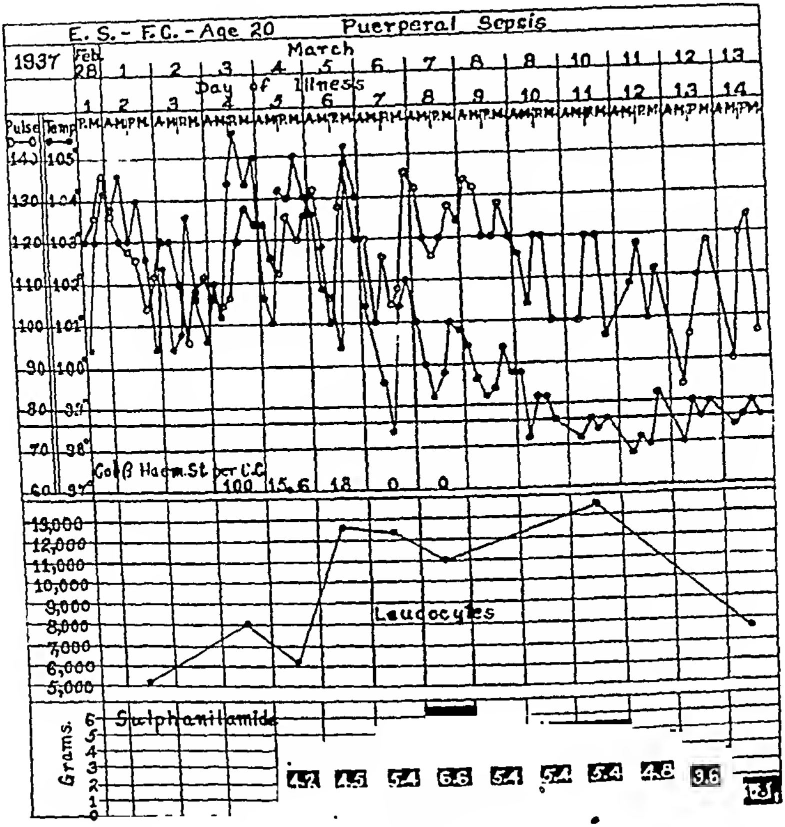

CHART 2.—A case of puerperal sepsis treated with sulphanilamide.

It is possible that some of these accessory factors are absent in the patients with streptococcal peritonitis which have been treated with sulphanilamide, for failures have been recorded in several instances.[10,40g] On the other hand, recoveries have been observed, and Dr. Edwards Park has allowed me to mention a case of peritonitis in a premature colored infant who 1 month after birth developed otitis media and peritonitis, due to β hemolytic streptococci. He recovered after repeated subcutaneous injections and 1 intraperitoneal injection of a solution of sulphanilamide combined with $\frac{M}{6}$ sodium lactate, in spite of the fact that repeated transfusions were necessary to combat a severe hemolytic anemia, produced apparently by the sulphanilamide. Colebrook and Purdie[13] report 2 recoveries out of 4 cases of peritonitis occurring in women with puerperal sepsis.

Indeed, the treatment of puerperal sepsis has been attended with highly satisfactory results. Colebrook and his associates[11–12], Foulis and Barr[22] and Gibberd[27] among others, have shown a very pronounced reduction in the mortality from puerperal infection due to β hemolytic streptococci with the introduction of prontosil and sulphanilamide. The results of Colebrook and Purdie[13] are particularly striking on account of their conservative attitude. The death rate for cases with positive blood cultures with or without peritonitis was reduced from a previous average of 71% to 27.3% in 22 cases treated with these drugs.

Chart 2 shows the essential features in a patient suffering from puerperal sepsis with positive blood cultures, who recovered after treatment at this hospital.

A colored woman of 20 was admitted to the obstetrical service of this hospital (Unit 100717) on March 1, 1937, having been delivered outside the hospital 6 days previously. Three days after delivery she had a "slight cold," and on the day of admission the lochia increased, she felt badly and had slight fever. She was found on admission to have a temperature of 103°, a red pharynx, and râles at the bases of the lungs. She appeared very ill. The blood pressure was 118/84; the leukocyte count 5200. The urine showed no albumin. A blood culture on March 3 showed 100 colonies of β hemolytic streptococci per cc. and she was transferred to the medical wards.*

The significant features of her illness are the early invasion of the blood, the rapid decrease in the numbers of colonies per cc. with a subsequent steady rise during the first days of sulphanilamide therapy, followed by a rapid disappearance of hemolytic streptococci from the blood, a fall in temperature, with a rise in leukocytes, and rapid recovery without complications.

Erysipelas is a disease which furnishes signs of advance or regression that are more or less readily measurable. One gains the impression possibly on this account that it is a form of streptococcal infection, which is very favorably influenced by the action of sulphanilamide. The literature contains accounts of hundreds of cases which have been treated, with few fatalities. It is usually stated that the spread of the infection is prevented and that the duration of the disease is shortened, the temperature falling within 24 to 48 hours after treatment is started.[54] Hageman and Blake[31b] give a duration for control cases of 13.9 days; for treated cases 5.3 days. Snodgrass and Anderson,[63] who report the results of treatment in 160 cases, state that the mortality was reduced from 9.6% in a control series of 312 cases to 2.5% for the cases treated with prontosil and sulphanilamide. Hageman and Blake include in their series 2 cases of erysipelas in infants, showing positive blood culture, with recovery. The results in these 2 patients are particularly striking, for under such conditions, the disease is almost always fatal in infants.

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* This case has been included by Drs. Long and Bliss in their statistics.[illegible]

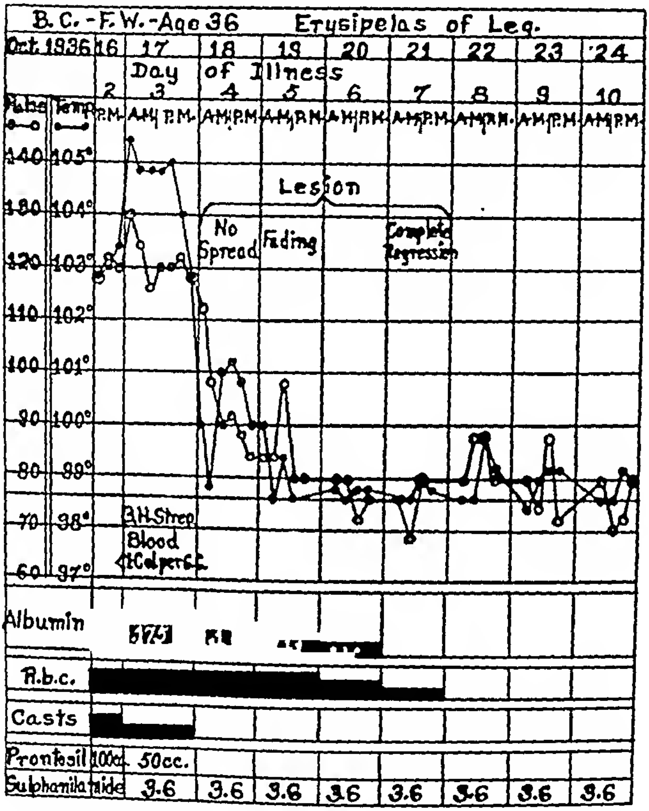

CHART 3.—A case of erysipelas treated with sulphanilamide.

Chart 3 illustrates the course of a rapidly spreading erysipelas treated with sulphanilamide.

A white woman of 36 years was admitted to the medical service of this hospital on October 16, 1936, complaining of a painful swelling of the leg. She had had an ulcer of the leg for 10 weeks. The night before admission, she had had a chill, fever, and a red, tender, painful swelling had appeared about the ulcer.

The small ulcer was about the size of a dime, surrounded by a fiery red, tender swelling. A brawny swelling showing red indurated areas and sharply defined margins extended from the ankle almost to the knee. The blood pressure was 110/70; the patient appeared very ill; leukocytes 12,000 (Chart 3).*

The significant features are the disappearance of hemolytic streptococci from the blood, the cessation of spread, the critical fall in temperature on the fourth day of disease, and the rapid recovery without complications under sulphanilamide therapy.

The conditions on admission were those that one usually associates with a rapid and very unfavorable progress. It will be remembered that in our control series 85% of such cases terminated fatally.

Scarlet fever presents clinical and immunologic problems (Francis[23]) that differ materially from those in erysipelas, and I have gained the impression that sulphanilamide has comparatively little, if any, influence upon the course of the acute illness. Hageman and Blake[31b] conclude from an analysis of 7 cases that the drug shows no effect in the toxic stage of the disease, though none of their patients developed complications. Peters and Havard[54] gained the impression that the number of complications was reduced in their treated cases. Possibly with further experience it may be possible to employ sulphanilamide more effectively in this disease, but from what we now know about the action of the drug, it is unlikely that the toxemia itself would be affected. One might, nevertheless, hope to obtain some relief of the local infection of the throat and thereby prevent the distressing and serious complications that so frequently follow scarlatina.

In our limited experience, however, it has proved difficult to rid the throat and tonsils of hemolytic streptococci by the use of sulphanilamide.

It has already been pointed out that recovery from a local streptococcal infection may take place without elimination of the organism from the point of infection. Colebrook and Purdie[13] found this to be true in puerperal infections of the uterus, and it is well known that after an attack of acute tonsillitis, hemolytic streptococci may remain in the tonsils for weeks or months.

In an attempt to hasten recovery from acute infections of the tonsils and throat by hemolytic streptococci in patients suffering from acute hemorrhagic nephritis, we have used sulphanilamide in 15 cases in moderate sized doses for fairly long periods of time. Cultures from the throat of all of these patients, before treatment was begun, showed moderate to great numbers of β hemolytic streptococci (Table 4). Cultures were made repeatedly during the course of treatment and from the interior of the tonsils from 13 of these patients who after treatment were subjected to tonsillectomy.

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* The case was included in the statistics published by Drs. Long and Bliss.[illegible]

The tonsils from 6 of these patients, who had received from 18 to 66 gm. of sulphanilamide over periods of from 6 to 25 days, and whose blood sulphanilamide varied from a concentration of 7 to 19 mg. %, showed a heavy growth of hemolytic streptococci, while in one other patient who had tonsillitis and sinusitis and who had received 39 gm. of sulphanilamide over a period of 12 days, cultures from the throat were almost continuously positive for 6 months. Four of these patients manifested mild symptoms of intoxication such as slight fever, headache, nausea, and cyanosis.

TABLE 4.—EFFECT OF SULPHANILAMIDE UPON LATENT INFECTION OF TONSILS BY HEMOLYTIC STREPTOCOCCUS.

No	Original culture.	Sulphanilamide.			Subsequent throat cultures.		Culture from tonsils at operation.	Toxic symptoms
		Total grams.	Days admin	Blood concent., mg. %.	+.	0.		
1	++++	18 0	6		1	1	No tonsillectomy	0
2	++++	58 2	6	6 4-7 7	3	3	++++ (pure cult.)	0
3	++++	42 9	17	7 0-19 8	2	2	++++ (pure cult.)	0
4	++	28 8	25	7 2	8		++++ (pure cult.)	0
5	+++	81 0	24	.		3	0	0
6	++	66 0	12		2	.	++++ 90%	+
7	++	39 0	12		3		No tonsillectomy	±
8	+++ (antrum inf.)	58 8	32	6 5-10 0	5	3	No tonsillectomy cults. from pharynx pos. for 6 months	0
9	++++	18 6	7	6 0-7 6	4	1	0	+
10	++	27 9	12	6 9-11 0	1	6	0	+
11	++	43 2	12	10 2-16 4	3	4	0	++
12	++++	20 7	4	9 7-10 0	1	2	No tonsillectomy	+++
13	+	45 0	9	.	.	4	0	0
14	+++	16 2	6		1	3	0	+
15	++++	19 0	5	.	2	3	++++	++

Six patients whose tonsils did not show hemolytic streptococci at operation, and 2 whose throat cultures became negative received from 16.2 to 81.0 gm. of sulphanilamide over periods of from 6 to 32 days, during which time the concentration of sulphanilamide in the blood varied from 6 to 16.4 mg. %. Six of these 8 patients had mild symptoms of intoxication.

It seems clear to us that the administration of even comparatively large amounts of sulphanilamide over considerable periods of time will not always eliminate hemolytic streptococci from persistent and latent infections of the tonsils. Swift, Moen, and Hirst[66] have had the same experience in their study upon tonsillitis in rheumatic patients, while Colebrook and Purdie[13] report that hemolytic streptococci were recovered from cervical swabs taken on discharge from the hospital in 39 of 81 (48%) of their cases of puerperal infection that had recovered under sulphanilamide, and that 6 of 35 patients (17%) still showed positive culture for hemolytic streptococci 3 to 6 weeks later. Indeed, this is found to occur even in experimental infections, for Levaditi and Vaisman[39] and Long and Bliss,[40b,c] as well as Colebrook and his associates,[12,13] have reported the persistence of latent foci of hemolytic streptococci in mice treated for long periods by sulphanilamide.

The difficulty of eradicating *hemolytic streptococci completely* from the focus or foci of infection may very well explain the recurrences and relapses that have been occasionally encountered in some patients after cessation of treatment by sulphanilamide. Unless the protective mechanism of the body is capable of resisting an exacerbation of the infection, a renewed invasion of tissues by hemolytic streptococci is likely to occur.

It is for reasons such as these that the surgical methods commonly employed in the treatment of infections should not be abandoned when sulphanilamide is employed. Free drainage of infected areas is undoubtedly beneficial, and all possible means should be used to assist the body to combat the invasion of organisms, the multiplication of which appears, from studies made up to the present time, simply to be suppressed by the action of sulphanilamide.

Sulphanilamide, first thought to be almost innocuous, is now known to produce at times a variety of unpleasant symptoms, and is for a few patients highly toxic. Little information can be gained concerning this phase of the subject from animal experimentation; for, except in enormous doses, it is almost harmless for laboratory animals (Raiziss,[55] Hawking[34]). Marshall, Cutting, and Emerson[43c] find that when the drug is administered orally it requires 3.8 gm. per kg. to kill 50% of mice, and that dogs have recovered from doses of 2 gm. per kg. This would be equivalent to a dose of at least ¼ of a pound of the drug in a person weighing 150 pounds. The dogs, however, that received the large doses, were salivated, vomited, had diarrhea, hyperpnea, excitement, muscular weakness, ataxia, and presented signs of stimulation and depression of the central nervous system leading to a condition of spastic rigidity of the limbs and hyperesthesia. All but one of 9 dogs recovered within 12 to 24 hours. Prolonged administration of sublethal doses did not produce any evidence of chronic intoxication in rats or dogs. The acetyl derivative to which the drug is partially changed in many animals appears to be more toxic than the original substance.

In man, on the other hand, a long series of toxic effects have been described.[10,31a,b,40b,c,g] The subject is of great importance though it is only possible to allude to it at this time. It is quite impossible to predict what toxic symptoms will become manifest in any particular patient. Some patients have taken 1.2 to 2.4 gm. of the drug daily for months without the slightest ill effects. Nevertheless, in a fair proportion of patients receiving larger doses of the drug there is cyanosis. Many patients experience malaise, anorexia, dizziness, somnolence, nausea, headache, and are depressed. Vomiting is not uncommon. These are symptoms which have been observed in animals intoxicated by the drug and are dependent, no doubt, upon a direct action of the chemical. Febrile reactions, with or without skin eruptions are frequently encountered and are difficult to interpret, for one may be puzzled to know whether the fever is due to the drug, to an exacerbation of the infection, or to the occurrence of a complication. Morbilliform, and erythematous eruptions have been described, occasionally progressing to a dermatitis exfoliativa.[19,24,28,31a,47,48,59] They may be precipitated by exposure to light.[50] One patient is described as having a violent attack of urticaria accompanied by difficult breathing which appeared after the first few doses of the drug.[58] Optic neuritis has been recorded.[7] The acute anemias with evidence of hemolysis are particularly alarming;[33,37] but when the drug is stopped and transfusions are given, recovery is extraordinarily prompt. The instances of agranulocytosis are more serious and deaths are reported as a result of this complication.[3,5,35,60,73]

Southworth[64] showed some time ago that the CO_2 combining power of the blood was almost regularly lowered and Marshall, Cutting, and Emerson[43c] have demonstrated experimentally that this is due to an acidosis associated with a disturbance in the acid base equilibrium. On this account sodium bicarbonate is administered regularly with sulphanilamide. The cause of the cyanosis is somewhat obscure. It may be associated with moderate degrees of hemoglobinemia or sulphemoglobinemia, but this does not appear to be sufficient to explain entirely the intensity of the bluish color that develops in many of these patients.[2,13,15,39,52]

Although the drug is excreted in the urine in considerable concentration, it does not appear to injure the kidneys.

In some patients, symptoms may appear after the first few doses of the drug. In other patients, they do not arise until the drug has been administered in full doses for several days. This is usually true of the "drug fever," which Blake[31a] pointed out was most likely to make its appearance between the seventh and tenth days after sulphanilamide had been started. Though a number of the toxic manifestations are to be attributed, as Marshall[43c] suggests, directly to the drug, others such as asthma, the acute anemia, and the agranulocytosis are so rare that they should be ascribed to a peculiar idiosyncrasy of the particular patient.

Most of the unpleasant symptoms, and especially those referable to disturbances of the nervous system, subside promptly when the drug is stopped and large amounts of fluid are administered. Under these circumstances, the fever usually returns to normal within 36 to 48 hours. The eruptions may persist for some days.

It seems obvious that when the drug is used for a specific purpose in a severely ill patient, it may have a remarkably beneficial effect and has undoubtedly saved many lives, but when it is used indiscriminately for minor ailments, it may prove ineffective, produce unpleasant symptoms and, in rare instances, be actually dangerous.

Conclusions. Hemolytic streptococcal infections, in which there is an invasion of the blood, the meninges, or the peritoneal cavity, are fatal in a large proportion of patients. The mortality in blood stream infections due to hemolytic streptococcal infections varied in 166 patients from 53.6% in mastoiditis and otitis media to 85.7% in erysipelas and cellulitis, while at least 95% of cases with meningitis succumb, and the mortality in peritonitis is perhaps still higher. Some factors contributing to this high mortality have been commented upon.

The pharmacologic and experimental action of sulphanilamide has been discussed, and the remarkable therapeutic effect of this drug in the serious infections due to hemolytic streptococci has been recorded. Attention has been drawn to the fact that it has a most pronounced effect in the early stages of these infections, but that it may fail to sterilize foci of latent infection in the tonsils. Some of the evidences of intoxication have been recounted, and it is pointed out that the most alarming of these are rare and probably depend upon an individual idiosyncrasy to the drug.

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STUDIES IN DIABETES MELLITUS.

VI. MORTALITY AND LONGEVITY OF DIABETICS.

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THE average length of life of diabetics has definitely increased in recent decades, particularly since the discovery of insulin. It is apparently still increasing. Reliable measures of this improvement, however, have been lacking. Until now the only method available has been to compare the average duration of the disease from onset to death among diabetics in successive calendar periods. This method is not statistically correct, but as long as the conditions of treatment and the mortality rate of diabetics were fairly stable, the result served as an approximation of the truth. But, when an important influence such as insulin came into being, the balance was upset, and the average duration of diabetes in fatal cases of recent years is no longer an accurate measure of the longevity of the diabetic. Indeed, such data on fatal cases alone may even mislead because they probably include an undue proportion of patients who were neglected or poorly treated, or who died of accidents or acute emergencies.

There are several other objections to the use of the average duration of the disease in fatal cases as a measure of longevity today: 1, In a group of diabetics under the care of any one physician or clinic, some of the patients were originally diagnosed elsewhere. These cases are the survivors of larger initial contingents of patients of other physicians. The longevity of the other patients of these physicians is unknown. The patients diagnosed elsewhere, therefore, have previous histories of diabetes of varying durations, many of them quite long. These cases artificially increase the average duration of the whole group. 2, The date of onset of diabetes is often not exactly determinable, and this may tend to increase or decrease the recorded duration of life of patients. 3, Cases with sudden onset and short duration of life are often not diagnosed and, therefore, do not get into the experience. This applies also to cases with somewhat longer durations, which because of lack of clear-cut symptoms of the disease are not recognized as diabetes. Somewhat different are certain other objections of a statistical nature. 4, When the data are classified by calendar year periods, deaths with longer durations are necessarily classified in the later periods and, consequently, boost the averages in those periods. 5, With a rapidly growing number of patients, even though the proportion of deaths to total cases may decrease, the actual numbers may go up. In this instance, the average duration of the fatal cases is relatively short, particularly so if there is a high selective death rate in the early years of the disease.

These defects in the method of average duration are clearly not all in one direction. They tend to counterbalance each other, but there is no way of telling how far this goes. In any event, there is an indefinite period of time, in the data based on duration from onset to death, in which no deaths can be recorded, because relatively few cases are diagnosed at the very onset of the disease. This is a serious matter in a mortality experience.

These many difficulties disappear only when the actual period of observation on each patient is recorded, and the longevity of the group is measured as for a population, or, more strictly speaking, when a survivorship experience of the type common in insurance work is computed. The fundamental unit is the year of life lived. This method permits the computation of death rates per head *per* *annum* at specific ages. Age is, of course, a vital factor in mortality. One can make comparable tabulations for as many groups as is warranted by the size of the group studied, as, for example, by sex, residence, occupation, and so forth. Details of this method of mortality analysis are not given here, but may be found in any of the standard textbooks dealing with the construction of mortality tables.* One special requirement in tabulating the data for a group of patients is that the follow-up must be practically complete. In the present instance of Dr. Joslin's patients, the follow-up has been carried out as fully as practicable and the number of "lost" or untraced cases in the group as a whole is less than 1% and in the special groups seldom, if ever, over 2%.

The present paper covers the total experience on all true diabetics treated by the senior author and his associates who were first treated in and discharged from the hospital during 1897 to 1928, or first seen at the office or in consultation during those years. These patients were traced to the anniversary in 1929 of their first hospital discharge or non-hospital observation, or to their pribr death except for pre-insulin cases surviving into the insulin period who have been traced to August 7, 1929, the anniversary of the date in 1922 on which the use of insulin was begun in the Baker Clinic. Desirable as it would be to have more recent data on all patients, the amount of time and labor of the medical staff of the Clinic required to trace successfully such large numbers of persons had become too great to be carried on. It was, therefore, decided sometime ago to limit follow-up efforts to special groups of patients who were of particular significance as illustrating the influence of important factors in the longevity of diabetics. Several such groups (*e. g.*, diabetic patients under age 40 at onset; diabetic physicians; and pre-insulin era patients) on whom more up-to-date information is available, will be reported in subsequent papers. The trend of the mortality of diabetics up to 1929, however, gives a sure indication that any changes since that date are changes of degree and not of kind. This will be found to be confirmed by the trends in the special groups which are next to be reported.

In the tabulation of the mortality experiences in this and later papers, untraced or "lost" cases were included up to the last date on which they were definitely known to be living. The years designated in the text and tables are "experience" or "exposure" years and not calendar years. The "experience" year includes the period from the date of the original observation in one year or the anniversary of such date to the anniversary in the following year. The tables exclude what may be called the "immediate" mortality, that is, patients admitted to the hospital or seen in consultation who were dangerously ill or moribund at the time and who died in the hospital during the first period of treatment there or within 1 week of discharge or within a week of first observation. The number of these "immediate" deaths in the experience reported here was 187, as compared with 2271 later deaths up to the 1929 anniversary.

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* For example, Murphy, R. D., and Papps, P. C. H.: Construction of Mortality Tables from the Records of Insured Lives, Actuarial Society of America, New York, 1922.

TABLE 1.—DEATH RATES PER 1000 AMONG DIABETICS IN THE NAUNYN, ALLEN AND BANTING ERAS. BY SEX AND ATTAINED AGE. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Sex; age.	1897–1913.			1914 to August 6, 1922.			August 7, 1922, to 1925.			1926–1928.		
	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.
Males.												
All ages . .	894	171	217.7†	3057	446	152.6†	3755	316	86.0†	4813	274	58.3†
Under 5 . .	1	2	1600.0	12	5	422.3	15	3	196.7	28	1	35.5
5– 9 . .	11	7	666.0	45	17	378.5	69	1	14.6	88	1	11.4
10–14 . .	11	10	951.5	48	18	375.1	94	6	64.1	153	—	—
15–19 . .	25	12	473.7	64	23	361.2	116	13	111.8	145	3	20.7
20–24 . .	15	6	389.1	90	15	165.8	123	16	130.6	159	2	12.6
25–29 . .	17	9	514.6	110	27	245.8	134	14	104.9	157	3	19.2
30–34 . .	39	7	181.8	103	20	195.1	150	12	80.0	241	7	29.1
35–39 . .	60	10	167.6	182	24	132.0	205	9	43.9	222	6	27.0
40–44 . .	82	17	207.1	234	30	128.0	278	6	21.6	357	8	22.4
45–49 . .	136	16	117.9	340	21	61.8	408	20	49.0	437	12	27.5
50–54 . .	124	14	113.4	472	46	97.4	513	31	60.4	602	36	59.8
55–59 . .	133	12	90.3	529	60	113.4	570	38	66.7	677	39	57.6
60–64 . .	123	21	171.1	384	55	143.3	504	62	123.1	653	48	73.5
65–69 .	77	18	232.8	234	45	192.1	317	41	129.4	514	52	101.1
70–74 . .	25	9	363.6	136	20	147.1	168	24	142.6	237	28	117.9
75–79 . .	15	1	65.9	58	10	274.7	67	14	209.8	115	20	174.3
80 and over	1	..	. .	17	4	238.8	25	6	241.6	30	8	269.6
Females.												
All ages . .	657	128	239.1†	2311	332	156.2†	3926	260	66.4†	5533	344	58.7†
Under 5 . .	2	1	571.4	13	3	227.8	16	1	62.2	24	—	—
5– 9 . .	5	11	2131.8	30	9	305.0	62	4	64.8	103	4	39.0
10–14 . .	17	6	351.1	46	19	410.8	88	4	45.7	142	4	28.3
15–19 . .	10	7	682.9	46	21	454.9	90	8	89.3	171	1	5.9
20–24 . .	9	8	865.8	34	23	676.7	42	1	23.6	112	5	44.7
25–29 . .	11	7	641.0	51	17	333.9	81	5	61.5	113	4	35.3
30–34 . .	30	7	234.6	76	19	251.1	114	9	79.1	150	6	40.0
35–39 . .	40	10	249.0	116	11	94.9	164	7	42.6	215	6	27.9
40–44 . .	43	6	138.5	168	22	131.3	249	10	40.1	345	8	23.2
45–49 . .	77	7	90.7	237	17	71.8	366	8	21.8	452	11	24.3
50–54	101	8	79.1	339	26	76.7	579	25	43.2	758	34	44.9
55–59 . .	96	9	93.8	415	30	72.4	718	46	64.1	948	51	53.8
60–64 .	53	15	280.8	375	36	96.0	608	48	79.0	807	60	74.4
65–69 . .	75	15	201.1	209	27	129.3	457	42	91.9	669	72	107.6
70–74 . .	51	7	137.3	93	23	247.6	213	21	98.4	360	44	122.2
75–79 . .	23	3	131.4	41	19	466.4	62	14	224.3	133	26	195.8
80 and over	13	1	75.0	25	10	405.4	16	7	441.9	32	8	252.6

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* Fractional parts of years of life exposed were tabulated but the exposed in this table are taken to the nearest whole numbers.

† Standardized on basis of patient population, 1897 to 1929.

Mortality of Diabetics During Three Eras of Treatment. Table 1 gives the years of life exposed, the number of deaths and the death rates per 1,000 of the diabetics in this experience. These facts are shown in detailed attained age groups and by sex during three separate periods, namely, the Naunyn era (experience years, 1897 to

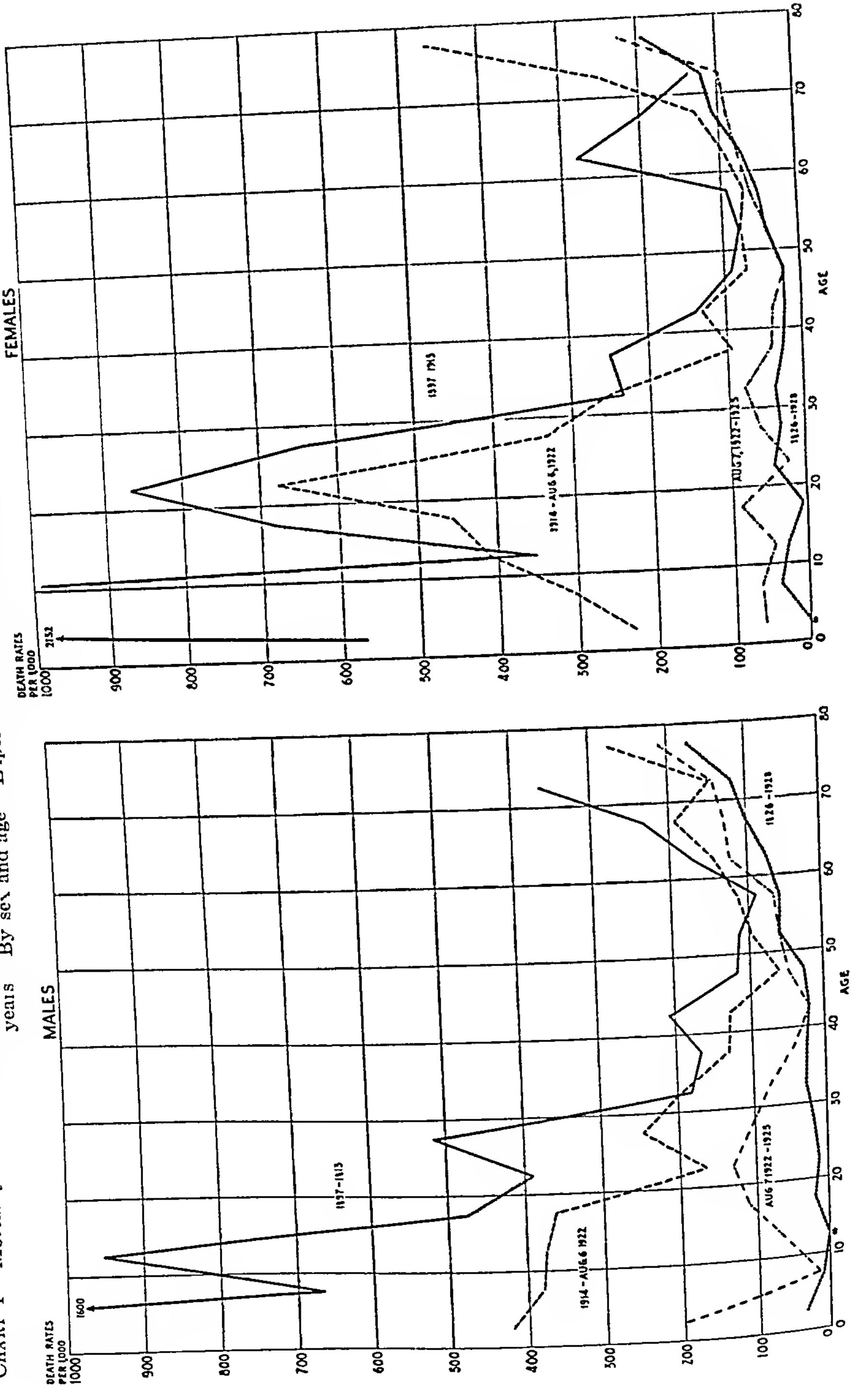


CHART 1 —Mortality among diabetics in the Naunyn, Allen and Banting Eras compared Death rates per 1000 in specified "experience" years By sex and age Experience of E. P Joslin, 1897 to 1929.

1913), the Allen era (1914 to August 6, 1922) and the Banting era (August 7, 1922, to 1928). The last is subdivided in two parts, the dividing line being the end of 1925, in order to show both the immediate effect of insulin on the death rates and the effect of the increased skill in handling it, resulting from its continued use.

TABLE 2.—PER CENT DECLINE IN DEATH RATES OF DIABETICS BETWEEN VARIOUS ERAS OF TREATMENT.* BY SEX AND AGE. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Sex; age.	Per cent decline in death rates between			
	Naunyn era and second part of Banting era.	Naunyn era and Allen era.	Allen era and first part of Banting era.	First and second parts of Banting era.
Total.				
All ages	74.4	32.4	50.6	23.2
Under 10	98.3	74.6	82.5	60.4
10–19	97.8	34.6	80.3	82.7
20–29	95.4	41.6	77.0	65.4
30–39	85.4	23.1	63.3	48.2
40–49	81.7	29.9	63.9	27.7
50–59	42.0	4.1	34.4	7.8
60–69	60.9	38.4	23.2	17.3
70 and over	30.0	+17.3	34.2	9.3
Males.				
All ages	73.2	29.9	43.6	32.2
Under 20	98.3	50.1	78.8	84.2
20–39	91.6	36.5	54.4	71.0
40–59	61.0	16.8	45.4	14.1
60 and over	53.9	21.5	20.1	26.5
Females.				
All ages	75.5	34.7	57.5	11.6
Under 20	97.7	56.4	82.8	69.6
20–39	91.7	33.7	81.4	33.1
40–59	57.6	13.8	44.7	11.0
60 and over	53.3	29.0	35.1	+1.3

* Naunyn, 1897–1913. Allen, 1914–August 6, 1922. Banting, first part, August 7, 1922–1925; second part, 1926–1928.

The experience within each of these periods includes the observations on patients surviving from earlier periods and on new patients entering into the experience during the period. Chart 1 gives a graphic representation of the observed mortality by age and sex.

Striking improvement in the mortality of diabetic patients is clear from the chart. It is greatest in children, amazingly so, but real improvement has taken place since the early years of this experience at every age and among both males and females. The minor exceptions that are found in the table and the chart may be discounted as accidental or fortuitous. It is remarkable how drastically and consistently the death rates of diabetic patients have fallen. It will be noted that among children the death rate prior to insulin occasionally exceeded 100% *per annum*. Actually, these extremely high rates represent a force of mortality rather than a true death rate, which cannot exceed unity. They indicate that the average duration of life among the children exposed in those age groups was less than a year after first observation. It is also clear that prior to 1914 the death rates among diabetics were highest at the very young ages. At that time the rates at every age up to 30 were much higher than those recorded between 70 and 80. Despite some improvement in the mortality of young diabetics in the Allen era, the death rates under 20 were generally higher than at all other ages, and between 20 and 30 were higher than between 30 and 70. With the introduction of insulin, however, there was a decided change for the better, and although very high rates still prevailed among the young diabetics, the rates were far lower than in the preceding eras. In the second part of the Banting era, the situation among young people improved still more, and for the first time the diabetic group yielded a mortality curve that was normal in respect to its shape, in that the lowest rates were recorded at younger ages and increased gradually through adult life.

The remarkable changes in the death rates among diabetics are shown in Table 2, which gives the percentage decline between successive periods and also between the first and last periods studied. The percentages at all ages combined were computed from death rates which were standardized on the basis of the total exposed to risk at each quinquennial age group from the beginning to the end of this experience. At all ages combined, the death rate in the second half of the Banting era was 74% less than in the Naunyn era. The death rate fell nearly one-third between the latter and the Allen era, but a much more rapid fall came as a result of the introduction of insulin, the death rate dropping 51% between the Allen and the first part of the Banting era, and 23% between the first and second parts of the latter era. These improvements apply to both males and females. The only notable difference is that the gains immediately following insulin were greater among females. Ultimately, however, the improvement as a result of the use of insulin has been about the same in both sexes.

Most impressive have been the declines among young diabetics. In the first two decades of life, the death rates in the second part of the Banting era were 98% below those in the Naunyn era. In other words, the rates in the later period were only about one-fiftieth of those prevailing prior to 1914. In the third decade, the drop was 95% and in the next two decades of life up to age 50 was over 80%. The smallest decline, 30%, was recorded in the eighth decade. In practically every instance, the rate of fall was greatest immediately after insulin was introduced. At ages under 30 the death rates in the early Banting era fell over 75%, that is, to levels less than one-fourth of those prevailing in the period immediately preceding. Continued and marked improvement has taken place at all ages throughout the Banting era, but again these changes were most marked at the younger ages.

As the table shows, the rates of improvement by age have been about the same in each sex. The more rapid decline among females in the early Banting period was most distinct at ages under 40, but this was counterbalanced by the more rapid decline among males at these ages in the later Banting period.

TABLE 3.—EXPECTATION OF LIFE OF DIABETICS IN THE NAUNYN, ALLEN AND BANTING ERAS.* BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Age.	Expectation of life (years).							
	Males.				Females.			
	Naunyn.	Allen.	Banting.		Naunyn.	Allen.	Banting.	
			First part.	Second part.			First part.	Second part.
10 . .	1.1	2.8	10.8	33.2	1.5	2.4	17.8	30.2
15 . .	1.7	3.6	10.2	31.0	1.6	2.0	18.0	27.6
20 . .	2.4	4.6	11.0	28.2	1.3	1.8	18.8	24.7
25 . .	2.5	5.1	14.0	25.4	1.6	3.0	17.7	22.9
30 . .	4.5	6.5	16.3	23.1	3.7	6.0	17.4	22.4
35 . .	6.3	8.4	17.4	21.0	6.0	9.2	18.7	21.5
40 . .	6.7	9.7	16.3	18.5	8.6	10.4	18.1	19.3
45 . .	7.7	10.0	13.6	15.5	9.3	11.1	16.1	16.5
50 . .	8.0	8.6	11.2	12.9	8.0	10.5	13.4	13.6
55 . .	7.0	7.1	9.4	11.2	5.8	9.2	11.1	11.1
60 . .	5.1	6.0	7.7	9.4	4.2	7.2	9.4	9.1
65 . .	+	5.4	6.5	7.7	+	5.3	7.7	7.4
70 . .	+	5.1	5.6	6.0	+	3.4	5.4	5.8

* Naunyn, 1897–1913. Allen, 1914–August 6, 1922. Banting, first part, August 7, 1922–1925; second part, 1926–1928.

+ Figures not reliable.

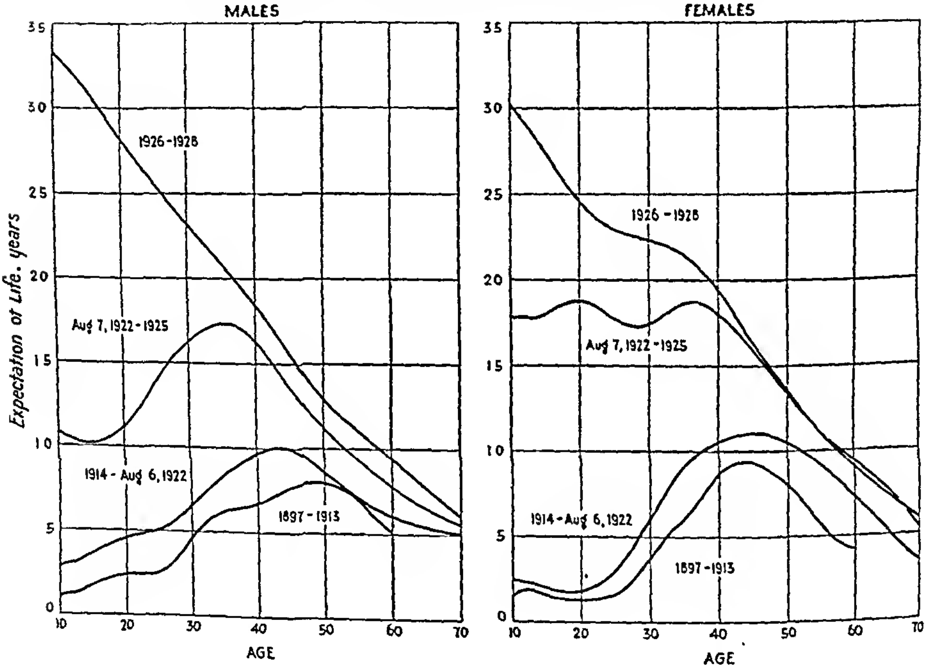
Comparative Mortality of Male and Female Patients. Male and female diabetics have approximately the same death rate. This is also brought out by Table 1. Prior to the discovery of insulin there was a moderate excess mortality among females, but with the discovery of insulin there was a sharp but temporary reversal in the relative mortality of the sexes. In the second part of the Banting era, however, the death rates at all ages combined were nearly identical.

There were, however, distinct variations by age. In all but one period the death rates of female patients under 40 have been generally higher than those for males. On the other hand, between 40 and 60 years of age, the death rates of male patients have been the higher. At ages over 60 the rates have been moderately close, except during the period immediately after insulin was introduced.

At that time the death rate of females at ages over 60 fell to a point 25% below that of males. It is notable that this is the only group in which the death rate in the second half of the Banting era showed no improvement over the earlier part.

The Expectation of Life of Diabetics. These striking reductions in the mortality of diabetic patients, of course, mean many added years of life. This is brought out clearly by Table 3 and Chart 2 which give the figures for their expectation of life, by age and sex, computed on the basis of the mortality rates shown in Table 1. These figures of expectation of life are presented as tentative and approximate only. They apply, at any specific age, to the diabetic of average duration of the disease in the several epochs of this experience, and not to those with onset at the age. In constructing a life table, it is implicitly assumed that the persons at any specific age will, in the future, experience the death rates observed at the later ages. The situation among diabetics, particularly in the earlier periods of treatment and at the younger ages, does not strictly conform to this assumption. But as against this defect, it may be noted that at those ages where the death rates were extremely high (as, for example, the pre-insulin rates under age 30 in Table 1) the expectations of life were little affected by the death rates at

CHART 2.—Expectation of life of diabetics in the Naunyn, Allen and Banting Eras. By sex and age. Experience of E. P. Joslin, 1897 to 1929.



ages much removed. So far as duration of the disease exercises any effect on the death rates, we have found that, under recent conditions of treatment, this effect is relatively slight at the middle ages for durations up to 15 years. For longer durations there is as yet no adequate information. There are extremely few middle-aged diabetics whose disease began in childhood or early adult life. Practically all of them must be post-insulin cases because of the high death rate among young diabetics previously. Too short a time has elapsed since insulin came into use in 1922 for any large number of younger diabetics to attain middle life. By the very nature of the problem, it will take at least a decade to get a sizable experience on such cases.

TABLE 4.—RATIOS OF DEATH RATES AMONG DIABETICS TO THOSE AMONG PERSONS IN THE GENERAL POPULATION AT SPECIFIED PERIODS OF TIME.* SELECTED AGE GROUPS BY SEX. DIABETICS IN EXPERIENCE OF E. P. JOSLIN AND PERSONS IN THE ORIGINAL REGISTRATION STATES.

Sex; age.	Ratios (death rates of population = 1.)			
	Naunyn era.	Allen era.	Banting era.	
			First part.	Second part.
Males.				
5–14	260.9	129.9	18 7	1.8
15–24	92.0	56.0	36.8	5.0
25–34	40.8	35.7	19.9	5.5
45–54	7.1	6.3	4.1	3.4
65–74	4.2	3.0	2.3	1.8
Females.				
5–14	263.4	147.8	28.2	17.3
15–24	179.0	122.0	21.3	6.6
25–34	54.5	42.5	16.3	8.6
45–54	6.5	6.2	3.1	3.4
65–74	3.1	3.0	1.8	2.2

* Diabetics in Naunyn era *vs.* O. R. S., 1910; in Allen era *vs.* O. R. S., 1920; in Banting era *vs.* O. R. S., 1925.

Substantial gains in expectation of life have been made at every age, but most of all at the younger ages. Thus at age 10, the expectation of life of a diabetic boy in the Naunyn era was a little over a year. In the Allen era it jumped to nearly 3 years, increased sharply to nearly 11 years in the period immediately following the discovery of insulin, and increased extraordinarily again to 33 years after insulin had been in use 4 years or more. Altogether the gain in expectation of life for a diabetic boy of 10 was over 30 years. A slightly smaller gain was recorded for girls at this age. At age 20, the expectation of life of male diabetics has gone up from less than 2½ years in the Naunyn era to over 28 years in the second part of the Banting era, an increase of nearly 26 years. The increase for females was slightly less. At age 40, the expectation of life for both male and female diabetics has more than doubled between the two periods, with gains of over 11⅔ and over 10½ years for males and females respectively. Even at age 60, the expectation of life of males has increased 4⅓ years, and that of females nearly 5 years.

Another interesting feature of the expectation of life figures is that prior to the discovery of insulin and even in the early years following that event, the age curve of expectation was grossly abnormal in shape. Normally, this curve is a steadily diminishing one, except during the first year or two of life when mortality rates are very high. In contrast, the earliest curves among diabetics show the highest expectation between 40 and 50 years of age. The two curves for males prior to insulin show increasing expectation from the youngest age in the table up to this maximum. The curves for females, after a slight initial decline also rise with age to a maximum in the 40's. In the first part of the Banting era, the male expectation of life increases up to age 35 before it begins declining, and the female curve fluctuates within a range of 1½ years up to age 36, with maximum figures at ages 20 and 36, before it too declines in the normal manner. In the second part of the Banting era, the curve is entirely normal in shape, declining progressively from the youngest to the oldest ages.

TABLE 5.—COMPARISON OF EXPECTATION OF LIFE OF DIABETICS AND PERSONS IN THE GENERAL POPULATION AT SPECIFIED PERIODS OF TIME. SELECTED AGES BY SEX. DIABETICS IN EXPERIENCE OF E. P. JOSLIN AND PERSONS IN THE ORIGINAL REGISTRATION STATES.

Sex; age.	Expectation of life (years).							
	Diabetics, Naunyn era.	O. R. S., 1910.	Diabetics, Allen era.	O. R. S., 1919–1920.	Diabetics, Banting era, first part.	O. R. S., 1919–1920.	Diabetics, Banting era, second part.	O. R. S., 1929–1931.
Males.								
10	1.1	51.3	2.8	52.8	10.8	52.8	33.2	54.5
30	4.5	34.9	6.5	36.5	16.3	36.5	23.1	36.9
50	8.0	20.4	8.6	21.4	11.2	21.4	12.9	20.8
Females								
10	1.5	53.6	2.4	53.8	17.8	53.8	30.2	57.1
30	3.7	37.0	6.0	37.6	17.4	37.6	22.4	39.3
50	8.0	21.7	10.5	22.3	13.4	22.3	13.6	22.7

Comparison With Population Tables. The great strides toward normality that the diabetics have made with respect to longevity are brought out by comparing the death rates and the figures for expectation of life of these patients with the data for the general population of the Original Registration States. The great majority of the patients in this experience were drawn from 8 of the 10 states, which comprise this area, namely, the New England States, New York, and New Jersey. The comparison might also have been made with Massachusetts figures but the results would differ little. Population data for calendar years conveniently close to the several eras of treatment have been used.

Table 4 gives the ratios at selected ages of the death rates of these diabetic patients to the rates in the general population. This shows that in the Naunyn era, *i. e.*, prior to 1914, the death rates of diabetic patients between the ages of 5 and 14 were over 250 times the corresponding rates for the general population. Between ages 15 and 24, male diabetics had a death rate over 90 times that of the general population and female diabetics, nearly 180 times. The ratios decreased progressively with age so that at 65 to 74 they were only 4 times the general population rates for males and a little over 3 times for females. These ratios of the mortality of diabetics to that of the population have declined very drastically. With but unimportant exceptions each successive period of treatment showed lower ratios at every age. In the second part of the Banting period, the highest ratios recorded at the younger ages were under 6 in the case of males. They were generally higher in the case of females, notably between ages 5 and 14. At the older ages the death rates of diabetics in the Banting era were only about twice those in the general population.

Table 5, which gives the expectations of life at selected ages of diabetics and of persons in the Original Registration States, shows what large gains the decline in the preceding ratios mean when translated into expectations of life and, at the same time, how far the diabetic yet has to go to have a normal expectation for his age. For example, the diabetic boy of 10 of the Naunyn era had an expectation of life of scarcely one year, compared to an expectation of 51 years in the general population at that age. There was thus a loss of 50 years for the diabetic boy. Despite a sizable gain during the Allen era, there was just as great a gain in the population figure and consequently the deficiency remained at 50 years. With insulin, however, there was a marked increase in the expectation of life of the diabetic child and by the second part of the Banting period the expectation of life for a diabetic boy of 10 reached 33.2 years, as compared with 54.5 for males aged 10 in the Original Registration States during 1929 to 1931. Thus, the loss had been reduced to slightly over 20 years. At every age and both among males and females, the expectation of life of the diabetic patient has increased much faster since insulin than that of the general population and considerable progress has been made in reducing the deficiency in his expectation of life.

Summary. Life tables have been constructed for diabetic patients treated at the Baker Clinic during 1897 to 1928 and traced to 1929. These tabulations have been made in the same manner as survivorship experiences in insurance work. Only the period under observation was included, *i. e.*, from first consultation or hospital discharge. These tables give a definite measure of the improvement in the treatment of diabetes.

The outstanding facts are: 1. There has been a continuous decline in the death rate of diabetics.

2. The death rate at all ages in the latter part of the period surveyed, 1926 to 1929, was 75% below that of the first part, 1897 to 1913.

3. The gains have been greatest in young diabetics.

4. The decline in mortality was most rapid after insulin came into use.

5. Large increases in the expectation of life have occurred. At age 10, the increase between 1897 to 1913 and 1926 to 1929 is estimated at about 30 years. The increase is progressively less with advancing age.

6. The death rates of diabetics are still much in excess of those for the general population.

THE CREATINE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF GRAVES' DISEASE AND ALLIED CONDITIONS.

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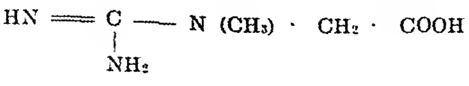
Ever since Shaffer[13] in 1908 reported significant creatinuria in patients with Graves' disease, occasional contributions to the study of creatine-creatinine metabolism in this disease have appeared. The more important of these include the observation of Palmer, Carson and Sloan[9] that creatinuria in Graves' disease disappears on the administration of iodine. More recently, Shorr[10,12] conceived the idea of putting a strain on the mechanism controlling creatine metabolism by causing the patient to ingest a known quantity of creatine. In this manner, the degree of excretion could be determined and a creatine tolerance test was devised.

Before describing the test and the clinical material forming the basis of this report, a short discussion of creatine-creatinine metabolism is presented.

Creatine. Creatine is methylguanidine acetic acid, whose chemical formula is

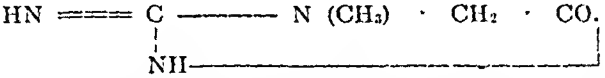


$$HN = \underset{\displaystyle NH_2}{\underset{|}{C}} - N(CH_3) \cdot CH_2 \cdot COOH$$

About 98% of the total amount in the body occurs in muscle, particularly striated, and most of the remainder in the brain. It is presumably derived from protein. Fiske and Subbarow[2] have shown that a large part of creatine in muscle is present in combination with phosphoric acid as phosphocreatine.

Creatine is present in the blood in very low concentration. It is claimed to be normally absent in the urine of human adults except during menstruation, gestation, and lactation; it may also be present during starvation and as a result of the ingestion of a high-animal protein or low-carbohydrate[7] diet. Creatinuria likewise is present in febrile and acidotic conditions, in hyperthyroidism, cretinism, infantilism, diabetes, achondroplasia, poliomyelitis, myositis, and other muscle diseases such as atrophy and dystrophy.[1]

Creatinine. Creatinine is the internal anhydride of creatine with the formula



$$HN = C - N(CH_3) \cdot CH_2 \cdot CO \quad (C\text{–}NH\text{–}CO)$$

Creatine can be converted to creatinine by removal of one molecule of water through treatment with hot acid solutions. The amount of creatinine in the 24-hour urine of normal adults ranges from .500 to 2.000 gm. Except for diet and exercise, it is a constant characteristic of a given normal individual,[3a] being determined by size and muscular development. For this reason, the total creatinine excretion is frequently employed as a means of checking the accuracy of 24-hour urine collections. Thus creatinine is apparently an end-product of creatine metabolism and merely represents a waste product. Ingestion of the substance results in almost quantitative excretion in the urine. This is in contrast to creatine, ingestion of which by normal adults results in about 70% retention.

Creatinine is increased in the urine in fevers and decreased in hyperthyroidism, diabetes and conditions of profound muscular weakness. It appears to be compensatorily lowered in the presence of spontaneous creatinuria.

Creatine Tolerance Test. The creatine tolerance test[10,12] was devised to determine the ability of persons on a creatine-free diet to retain ingested creatine. According to Shorr, evidence of a defect in the metabolism of this substance is indicated by: 1, spontaneous creatinuria above 50 to 60 mg. per 24 hours; 2, retention of less than 70% of the ingested creatine; 3, low output of creatinine per kilo of body weight.

Technique. The patient is placed on a creatine-free diet* for 4 days. During the third day he collects the entire urinary output for 24 hours under thymol. He then takes 1.32 gm. of creatine hydrate (equivalent to 1 gm. of creatine in the urine expressed as creatinine) dissolved in 180 cc. of water and the urine is again collected for 24 hours under thymol. The

* No fowl, fish in any form, meat or meat products such as soups, cocoa or chocolate.

entire urinary output for the control-day and the creatine-day is then analyzed for creatine and creatinine.

Method for Determination of Creatine and Creatinine. The method for the determination of creatine and creatinine was a slight modification of Folin's[3b]

Measure the volume of urine and pipette 2 cc. of the specimen (the amount required varies according to the creatinine in the specimen; it may be necessary to repeat with 1 to 5 cc.) in 100 cc. volumetric flask for preformed creatinine, and 2 cc. in 250 cc. Erlenmeyer for the "total creatinine."

To the Erlenmeyer flask add 20 cc. of saturated solution of very pure picric acid, an antibump tube, and record the weight of the flask and contents. Add about 150 cc. of distilled water and boil on an electric hot-plate until the flask and contents weigh about the original amount.

Compare both the "total creatinine" and preformed creatinine with standards containing 1 and 2 cc. of standard creatinine solution (containing 1 mg. of creatinine per cc.) in 100 cc. flasks. To standards and urine for creatinine add 20 cc. saturated picric acid. To all flasks add 1.5 cc. of 10% sodium hydroxide solution, and after 10 minutes transfer the hydrolyzed specimens from the Erlenmeyer flask to 100 cc. flask. Make up to mark with water and read immediately in colorimeter with the appropriate standard set at 10 mm.

The hydrolyzed specimen contains "total creatinine"—preformed and hydrolyzed creatine. The unhydrolyzed specimen contains preformed creatinine. So-called creatine is the difference between the total and unhydrolyzed specimens.

The creatine excreted on the second or creatine-day minus that excreted on the first or control day gives the amount of extra creatine excreted. This divided by the total amount of creatine which might have been excreted (1 gm.) gives the percentage excretion from which the retention is easily calculated. Normal adults are said to retain 70% or more.

Clinical Data. In order to determine the usefulness of the creatine tolerance test, it was performed in 75 patients with one or more of the following conditions: Graves' disease, autonomic imbalance, menopause, hypertension, non-toxic goiter and psychoneurosis. The patients were studied chiefly in the Out-Patient Department and were subjected to 102 tests. The individuals were classified in the following groups:

	No of patients.	No. of tests.
Graves' disease	15	27
Autonomic imbalance	42	57
Menopause with autonomic imbalance and hypertension	7	7
Essential hypertension	6	6
Non-toxic goiter	5*	5*
Psychoneurosis	1	1
	75	102

* One is included in the hypertension group.

At times the clinical diagnosis was not readily apparent and the patients required variable periods of observation. This was particularly true in the differentiation of Graves' disease from autonomic imbalance where it was sometimes necessary to hospitalize the patient for this purpose. The attending physician in charge of the service corroborated the final diagnosis in all such patients.

Many precautions were taken to insure accuracy on the part of the patient in performing the test. The creatine-free diet and the manner of collection of the urine specimens were explained to each patient in great detail. The patients were greatly impressed with the amount of attention they received and were uniformly coöperative and conscientious in the execution of the tests. In addition, they received printed instructions on the reverse side of which they were requested to keep a diary of the food eaten daily. When the patient brought the urine specimens back to the hospital, his accuracy

TABLE 1.—GRAVES' DISEASE.

Case No.	Sex.	Age.	Basal metabolic rate.				Creatine tolerance test.				
							Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
							Control day.	Creatine day.	Control day.	Creatine day.	
57	M	35	+59	+41	+52	+6*	0	0 050	0 640	0.950	95
58	M	52	+37	+31	_+20_	_+10_	.185	210	.880	.750	98
			_+28_	_+13_	−8	+31	.075	.365	.800	.390	71
			_+31_	_+41_	_+50_	_+29_					
			_+31_	+9†							
59	F	58		+48	_+17_		.145	.775	670	.615	37
60	F	45	+66	+52	+48	_+42_	0	.210	.570	1.170	79
			_+25_	+43	+24		0	.190	740	.945	81
							_.455_	_.905_	_.365_	_.795_	_55_
							0	.305	.805	.800	69
62	F	21	+35	+49	_+37_	_+21_	_.440_	_.705_	_.530_	_.445_	_74_
			_+8_	+50	0†	+25	.100	400	.710	.850	70
63	F	19	+15	+54	_+62_	_+64_	.050	.400	.435	.670	65
			_+38_	_+13_†	_+9_*		.180	.695	.815	.695	48
							.095	.115	.755	.785	98
64	F	56	+36	+29	+20		.045	.560	.450	.560	49
65	M	42	+60	+16	+51	_+60_	.175	1.190	1.150	.970	−1
			_+45_†	_+16_†	+4*	+9*	.025†	.645	...	...	38
							0*	.125	.840	.900	87
66	F	69	+51	+29	+43	_+34_	.390	1.885	.755	.765	−60
			_+24_	_+29_	_+22_	_+13_†	_.320_	_.390_	_.700_	_.665_	_93_
			_+22_	_+20_	+7	+47	_.305_†	_.340_	_.765_	_.790_	_97_
			−4	+23			.096†	.380	.720	.710	72
67	F	30	+62	+48	_+11_	_+28_	.260	.395	1.060	1.015	86
			+43	+48	+19†						

INACTIVE GRAVES' DISEASE.
Asymptomatic.

68	F	31		−13			.130	.420	.790	830	71
69	F	38	+66	+37	+43	+31	0*	.175	.920	975	82
			+45	+54	+27	+25*					

INACTIVE GRAVES' DISEASE.
Symptomatic.

70	F	27		+9	−4		.055	.210	775	.675	85
71	F	39			+14		.050	.815	975	895	23
73	F	48	+48	+47	−10	+6	0	.055	900	850	94
			−10	−6							

Figures in italics indicate determinations made during a hospital stay as an in-patient.

* Postoperative. † After lugolization.

was checked by a complete recital of the manner in which the voidings were collected. Tests were discarded in the event of error. While we occasionally noted the presence of significant variations in the output of creatinine in the 2 test days, we were prompted to include these tests for two reasons; first, because of our conviction regarding the reliability of the urine collections and second, because of the possibility that such variations may be inherent in the diseases investigated. Whenever possible attempts were made to repeat positive tests. Care was taken to exclude patients with acetonuria or with those physiologic and pathologic states known to induce creatinuria.

Shortly after this work was started, and in accordance with the experience of our Department of Chemistry, spontaneous creatinuria was not held to be abnormal nor was it so designated unless the creatinine exceeded 100 mg. in 24 hours. Tolerance to the ingested creatine was regarded as decreased when the retention was less than 70%. The finding of spontaneous creatinuria *or* decreased tolerance is referred to as a *partially* positive test while the presence of both indicates a *completely* positive test.

Graves' Disease. There were 15 patients in this group (Table 1), 10 active and 5 inactive as a result of operation or roentgentherapy. Of the 5 inactive cases, 3 were still symptomatic in that they still complained of nervousness, emotional and vasomotor instability and weakness, although the basal metabolic rates were normal and they had gained weight. The remaining 2 inactive cases were completely asymptomatic.

Of 10 patients with active Graves' disease, subjected to 22 tests, 8 had spontaneous creatinuria (Table 2). In 2 of these 8, it was present and in 3 others of these 8 it was absent on a second determination without the use of iodine. Six patients showed a decreased creatine tolerance. In 2 of these 6 it was present and in 3 it was absent on a second determination without the use of iodine. Spontaneous creatinuria *or* decreased tolerance was demonstrated in 9 patients, whereas *both* spontaneous creatinuria and decreased tolerance were found in 5. In 3 of these 5 patients, however, another test was entirely normal.

TABLE 2.—RESULTS OF CREATINE TOLERANCE TEST.

	Graves' disease.		Autonomic imbalance (49 cases).	Hypertension or goiter or psycho-neurosis (11 cases).
	Active (10 cases).	Inactive (5 cases).		
Spontaneous creatinuria	8	1	16	2
Confirmed by 2d test	2		4	0
Unconfirmed by 2d test	3		6	2
Decreased tolerance	6	1	18	1
Confirmed by 2d test	2		2	0
Unconfirmed by 2d test	3		6	1
Spontaneous creatinuria *or* decreased tolerance	9	2	27	2
Spontaneous creatinuria *and* decreased tolerance	5	0	5	0
Confirmed by 2d test	..		1	
Unconfirmed by 2d test	3		3	

Of 3 patients with inactive, but symptomatic, Graves' disease, none showed spontaneous creatinuria while one revealed decreased

Case No.	Sex.	Age.	Basal metabolic rate.	Creatine tolerance test. Creatine in grams per 24 hours. Control day.	Creatine tolerance test. Creatine in grams per 24 hours. Creatine day.	Creatine tolerance test. Creatinine in grams per 24 hours. Control day.	Creatine tolerance test. Creatinine in grams per 24 hours. Creatine day.	Retention, %.
2	F	39	+37 +65 −15	0 135	0 415	0.670	0.605	72
3	F	35	*	055	.635	.970	.720	42
4	F	30	+4	0	090	.900	.960	91
5	F	26	−10	0	330	.640	385	67
				030	135	.365	240	89
6	F	46	+38 +15	160	.730	.800	.970	43
				230	330	860	900	90
7	F	31	+33†	265	330	1 150	.850	91
8	F	36	+11 +43	105	780	535	.580	33
9	F	29	+42 +13	0	630	1 270	930	37
10	M	30	+3	095	190	1 845	1.160	91
11	F	45	+3	0	360	500	.530	61
12	F	59	+45 *−2*	0	165	750	.505	83
13	M	36	−3	0	0	1 040	1 280	100
14	F	37	+24 +23 +36 +15	055	700	1 275	1 240	36
15	F	40	+9	0	.125	955	1 290	87
				695	1 000	1 270	1 240	70
16	M	35	+22 +42 +23 *+17*	*070*	*655*	*910*	*990*	*41*
			+10 +5 +4 *+2*	*0*	*180*	*1 310*	*1 950*	*82*
			+31 +25 +14	0	335	1 590	1 850	66
17	F	45	+36 +49 *−20* *+5*	0	245	1 220	1.165	75
			+31 +11					
18	M	44	+17 +1	285	340	940	.785	95
				180	190	835	1 690	99
19	F	44	0	090	380	800	.710	71
21	F	26	+114† +31 +40 +17	0	135	560	830	86
			+47 +3 +5					
22	F	29	+64 *+37* *+30* *+19*	*170*	*220*	*440*	*.245*	*95*
			+25 *+20* +5	*155*	*605*	*580*	*.660*	*55*
				0	170	880	680	83
23	F	59	+33 +2 −6 +1	595	.935	895	.945	66
				210	875	855	.875	33
24	F	30	+11 −11	0	.150	.790	.620	85
25	F	19	−3	0	120	.740	.690	88
26	F	31	+46 +30 +35 +21	200	370	1 470	1.120	83
			+54 +23 *+9*	0	170	1 130	1 090	83
27	F	33	+22 +38 +15	145	445	835	810	70
				0	.280	870	1 050	72
29	F	25	+28 +14	0	120	.850	1 060	88
32	F	29	+71 +37 +29 *+9*	060	.495	750	825	56
33	F	38	+12	055	120	1 110	795	94
34	F	29	+16 +43 +2	040	080	.740	980	96
35	F	40	+2	070	420	620	1'400	65
36	F	74	+41 +30 +16	120	.100	470	660	102
				0	.450	1 200	1 200	55
38	F	28	−5 +19	055	090	730	660	97
39	M	40	+42 +4	135	320	1 025	1 470	82
				0	0	1 450	1 640	100
40	F	37	+23 0	165	520	985	860	65
				0	.295	960	835	70
41	M	43	+21 −16	.355	.490	1 415	730	87
42	F	33	+30 +18 0	0	.180	730	650	82
43	F	40	+10	.295	535	875	805	76
				.080	340	500	430	74
44	F	64	+20 +23 +20 +10	.065	195	745	885	87
45	F	33	+30 +45 +2	.130	.400	830	600	73
47	F	38	+28 +12 +43 +26	060	180	770	1 000	88
48	F	55	+20 +20 0	0	0	850	1 330	100
49	F	42	*+21* *+16* −8 +31	0	.365	625	475	63
			+18 +56 −2					

Figures in italics indicate determinations made during a hospital stay as an in-patient.

* Patient was too nervous to complete the test. Obviously not a case of Graves' disease.

† Obviously a false reading. Clearly not Graves' disease.

tolerance. Of the 2 inactive, asymptomatic cases, 1 disclosed spontaneous creatinuria while neither had a decreased tolerance.

Autonomic Imbalance. The patients in this group form a clinical entity which has been variously designated in the literature as "forme fruste" of hyperthyroidism, larval hyperthyroidism, Basedowoid, neurocirculatory asthenia, and Graves' constitution.[8] Kessel and Hyman[6] applied the term "autonomic imbalance" to this group of patients "whose symptoms can be ascribed to a disturbance in the realm of the involuntary nervous system. . . . Manifestations of the disturbance have been present in most of these patients as far back as they can remember."

The symptomatology is referable to that organ system whose involuntary innervation is disturbed. The dominant manifestations may thus be neuropsychiatric, circulatory, cardiac, gastro-intestinal or any combination of these. The commoner features of this syndrome consist of palpitations, dyspnea, tachycardia, labile pulse rate, tremor, sweating, vasomotor and emotional disturbances, nervousness, asthenia, anxiety states, diarrhea, "indigestion," menstrual disturbances, headache and insomnia. Non-toxic goiter is not infrequently present with such profound vasomotor disturbances as to simulate Graves' disease very closely. Even in the absence of goiter, differentiation from Graves' disease often requires prolonged observation. At times, hospitalization and patient effort to secure the subject's confidence is necessary in order to obtain accurate basal metabolic and pulse rates. Failing this, a therapeutic test with iodides usually aids in differentiation.

This group numbered 42 patients who were subjected to 57 tests (Table 3). Spontaneous creatinuria (the highest was 695 mg.) was found in 16 patients. In 4 of these, this was confirmed by a second test, while in 8, confirmatory results could not be obtained. Decreased tolerance was revealed in 15 patients. It was present in 2 and absent in 6 on a second determination. Either spontaneous creatinuria *or* decreased tolerance was disclosed in 24 patients. Spontaneous creatinuria *and* decreased tolerance were noted in 5 patients. The test was repeated in 4 of these and provided confirmation in but 1. A completely normal result was obtained in another. In 2 others, spontaneous creatinuria was again demonstrated but this time with normal tolerance. Three tests performed in 1 patient (Case 22) gave widely different results, ranging from completely normal to completely abnormal.

Menopause with Autonomic Imbalance and Hypertension. Autonomic imbalance is frequently observed in association with menopausal symptoms and hypertension, the latter usually of recent origin. In addition to menopausal vasomotor disturbances such as hot flashes, sweats and dizziness, this group of patients presents manifestations of dysfunction in the autonomic nervous system as outlined above. Here again differentiation from Graves' disease is occasionally difficult.

TABLE 4.—MENOPAUSE WITH AUTONOMIC IMBALANCE AND HYPERTENSION.

Case No.	Basal metabolic rate.	Creatine tolerance test.				
		Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
		Control day.	Creatine day.	Control day.	Creatine day.	
50	+21 +18 +5	0	0.365	1.065	1.100	63
51	+9 +5	.055	.410	1.275	1.090	64
52	+15 +35 +61 +12	.080	.200	.530	.695	88
53	+16 +41 +13 +48 +15 +32 +31 +38 +33	.045	.130	.880	.725	92
54	+9	.070	.100	.790	.905	97
55	+35 +26	0	.020	1.050	.720	98
56	+36 +25 −3 −5	.070	.390	1.250	1.060	68

There were 7 cases in this group (Table 4). By the creatine tolerance test, spontaneous creatinuria was absent in all, while decreased tolerance was found in 3.

TABLE 5.

Case No.	Sex.	Age.	Basal metabolic rate.	Creatine tolerance test.				
				Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
				Control day.	Creatine day.	Control day.	Creatine day.	
			Essential Hypertension.					
75	M	15	−28 −3	0	0.165	0.920	1.025	83
76	M	55	+25 +10 +19	0	.280	1.350	1.210	72
77	F	60	+27 +25 +20 +24 +12	0	.205	.925	.990	79
79	F	48	+31 +14	.015	.020	.365	.415	100
80	F	42	+26 +10	0	.190	1.055	1.090	81
83	F	44	0	.050	.100	.920	.535	95
			Non-toxic Goiter.					
77	F	60	+27 +25 +20 +24 +12	0	.205	.925	.990	79
84	F	15	+27 +6	0	.275	.890	.665	72
85	F	48	+18	.255	.380	1.670	1.220	87
				.070	.335	1.235	1.000	73
86	F	26	+13 +18	.330	.350	.650	.960	98
				.090	.530	.670	.625	56
87	M	18	−1	.070	0	1.360	1.775	107
			Psychoneurosis.					
91	F	32	−24	.060	.265	.305	.370	79

The results of the creatine tolerance test in this and the preceding group of cases of autonomic imbalance were combined (Table 2). Of the total number of 49 cases, spontaneous creatinuria occurred in 16 patients, decreased tolerance in 18, spontaneous creatinuria *or* decreased tolerance in 27 and spontaneous creatinuria *and* decreased tolerance in 5.

Hypertension or Non-toxic Goiter or Psychoneurosis. A group of 11 "non-nervous" patients was likewise subjected to the creatine tolerance test. These groups were selected because they are allied to the previous groups and yet may serve as controls.

The test was completely normal in 6 cases of hypertension (Table 5). Of 5 patients with non-toxic goiter (one was included in the hypertension group), spontaneous creatinuria was found in 2, but could not be confirmed by a second determination. One patient showed decreased tolerance which also could not be confirmed. Spontaneous creatinuria *or* decreased tolerance was present in 2 patients. The test in 1 patient with psychoneurosis was normal. Thus, of 11 patients, unconfirmed spontaneous creatinuria was found in 2, unconfirmed decreased tolerance in 1 and spontaneous creatinuria *or* decreased tolerance in 2. In no case were both spontaneous creatinuria *and* decreased tolerance present (Table 2).

Discussion. Our experiences with the creatine tolerance test are at variance with those recorded by Shorr and Thorn.[15] In the first place, only one-half of our active cases of Graves' disease gave a *completely* positive test. Attempts at confirmation of the positive test failed in each of 3 patients. On the other hand, a partially positive test (spontaneous creatinuria *or* decreased tolerance) occurred in 90% of these patients. Here again, however, when the test was repeated, confirmation was usually not obtained.

Shorr,[11] in reviewing our protocols, drew attention to the possibility of an unsuspected source of iodine, such as iodized salt, as an explanation for the absence of spontaneous creatinuria in some cases of Graves' disease. This cannot be denied but we feel that it is not of very great moment, inasmuch as Kepler and Boothby[5] found creatinuria in only 84% of 25 patients with Graves' disease who had not received iodine and in 60% of 115 similar patients of whom nearly two-thirds had received iodine. The former finding corresponds to our finding of 80% incidence of creatinuria in non-iodized Graves' disease.

The group of non-nervous patients comprising hypertension, non-toxic goiter or psychoneurosis, although small, may serve as a control series. Kepler and Boothby[5] have previously reported creatinuria in 11% of their cases of benign adenoma and in 14% of control cases. Tolerance tests were not performed by these workers.

In our series a *completely* positive test was not encountered in any case. A definite percentage, however, showed a *partially* positive test. Again, this was more often unconfirmed than confirmed.

Doubt is thus seriously cast upon the significance of partially positive results. In this connection, the work of Taylor and Chew[14] suggests that the occasional finding of spontaneous creatinuria in normal persons may be due to sudden, but not necessarily extreme, change in muscular activity.

The outcome of the test was most interesting in the group of patients with autonomic imbalance. More than one-half showed a *partially* positive test while in 10% a *completely* positive test was obtained. Thus, with respect to defects in creatine metabolism, this group occupies a position which is roughly midway between Graves' disease on the one hand and normal persons on the other (Table 2).

From our results it is apparent that this test is not constantly positive or pathognomonic in patients with Graves' disease. Furthermore, the occurrence of *partially* positive tests in a control series and *completely* positive tests in autonomic imbalance detracts from the usefulness of the test in differentiating borderline cases. Shorr contends that the specificity of the test in Graves' disease dwells in the disappearance of the positive test under iodinization. While we do not deny the fact that iodinization diminishes creatinuria in Graves' disease, our protocols indicate that a positive test, regardless of the disease, usually disappears spontaneously. On the other hand, our studies indicate a relationship between autonomic imbalance and Graves' disease which was postulated by Hyman and Kessel[4] but heretofore factually unconfirmed. It is their contention that Graves' syndrome represents a superimposition of hyperthyroidism on a fundamental imbalance of the autonomic nervous system. This is in keeping with the almost universally elicited detail in the history of patients with Graves' disease to the effect that the individual was "always nervous," "highstrung," "unstable," or neurotic. Of the 86 cases of autonomic imbalance studied by them, 1 patient was observed to pass into Graves' disease. Our own series is too small and the period of observation too short to permit comment on the incidence of this transition. However, the occurrence of the same metabolic defect (completely positive creatine tolerance test) in autonomic imbalance as in Graves' disease points to a fundamental relationship between the two. The fact that the defect occurs more often in the latter is due to the added thyroid disturbance.

Summary and Conclusions. 1. The creatine tolerance test as devised by Shorr was performed in a group of patients with one or more of the following conditions: Graves' disease, autonomic imbalance, menopause, hypertension, non-toxic goiter and psychoneurosis.

2. A small percentage of partially positive tests (18%) was encountered in the "non-nervous" control series composed of hypertension, non-toxic goiter and psychoneurosis.

3. A greater incidence of partially positive tests (37%) and a 10% occurrence of completely positive tests was encountered in the group of patients with autonomic imbalance.

4. The greatest frequency of positive tests (90%) was observed in the group with active Graves' disease.

5. Whereas a completely positive tolerance test may be useful in differentiating Graves' disease from a condition which does not at all simulate it, the efficacy of the test in the differential diagnosis of borderline cases, *i. e.*, autonomic imbalance, is sharply curtailed by the following observations; the occurrence of partially positive tests in control series and of completely positive tests in patients with autonomic imbalance; the occurrence of completely positive tests in *only* one-half of our patients with active Graves' disease.

6. The occurrence of completely positive creatine tolerance tests, indicative of a defect in creatine metabolism, in autonomic imbalance and Graves' disease suggests a fundamental relationship between the two.

We are indebted to Miss Mildred Rosenbluth for valuable assistance in the Clinic.

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THE COEXISTENCE OF MYXEDEMA AND PELLAGRA IN THE SAME PATIENT.

WITH REPORT OF TWO CASES.

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THE coexistence of pellagra and myxedema has not been reported as such in the literature. Either disease may be overlooked if the two coexist because of the similarity of the gastro-enteric, psychic, neurologic, and to a less degree, the dermatologic manifestations of the two maladies. Such an oversight may lead to a fatality, whereas otherwise recovery might be expected. It is for this reason that the following 2 cases are reported.

Case Reports. Case 1. A white married female, aged 53, entered the University Hospitals complaining of soreness of mouth, diarrhea, dryness of skin and hair, loss of the use of her legs, and mental changes. The history was questionable because of psychosis, but the general facts were confirmed by the family. She had always enjoyed good health and had reared 5 children. The present illness began 11 years before admission. The initial subjective manifestations consisted of increasing obstipation, weakness, drowsiness, intolerance to cold, absence of sweating, dryness of skin and hair, with loss of the latter from the axillæ, being suspicious of others, slowness of speech, and huskiness of voice. During the past 6 months soreness of mouth, diarrhea with 6 to 7 watery stools daily, dermatitis confined to the exposed areas, slight bilateral deafness, a vague paresthesia which progressed to abasia, and hallucinations appeared. The dietary history was of no value.

She was a well developed and nourished woman of about the stated age, who coöperated well and answered questions freely. The significant objective manifestations were slowness of speech, huskiness of voice, dryness and coarseness of hair which was absent from the axillæ, dryness of skin, brownish dermatitis over anterior legs and over dorsum of hands and forearms, slight bilateral deafness, marked stomatitis, enlargement of tongue with atrophied papillæ, cardiac rate of 70 beats per minute, arterial pressure 100/70, moderately distended abdomen, hemoglobin of 65%, erythrocytes 2.5 million, leukocytes 5200, achlorhydria, and a basal oxygen consumption of 45% below normal. Sluggish reflexes were the only neurologic finding in spite of the abasia. Blood agglutination reactions were negative for typhoid, paratyphoid, melitensis, and dysentery bacilli. There was no gross or occult blood in the stools and direct and cultural examinations revealed no pathogenic organisms. Roentgen-ray examination of the colon by barium enema showed a large atonic bowel.

Course. In order to ascertain which of the manifestations could be attributed to myxedema and which to pellagra, the hypothyroidism was controlled by the administration of desiccated thyroid gland and the pellagra permitted to continue by feeding a diet low in vitamins. The basal oxygen consumption increased to 2% above normal at the end of 3 weeks, and the weakness, drowsiness, and intolerance to cold subsided. Sweating appeared and the speech improved. The psychosis improved remarkably, but the diarrhea, stomatitis, and dermatitis persisted.

A high-caloric, high-vitamin diet with added vitamin B, and a maintenance dose of desiccated thyroid gland were then prescribed. She ate fairly well and during the next 5 weeks the dermatitis and stomatitis disappeared, the mental condition continued to improve, but the diarrhea persisted. During the next 12 weeks, in spite of large amounts of liver extract parenterally and yeast and liver extract orally, the psychosis returned, delusions and hallucinations appeared, and all attempts to maintain an adequate food intake failed. She lost body weight and the mental condition necessitated that she be transferred to the Psychopathic Hospital. The appetite immediately improved and during her stay of 3 weeks she gained strength and body weight, and the diarrhea subsided. The psychosis, however, continued and she was transferred to the State Hospital for the Insane. The psychosis gradually subsided and after 3½ months she was permitted to return home. A report by letter after 4 months at home stated that she felt well and was doing her own housework.

Case 2. A white married female, aged 38, entered the University Hospitals complaining of weakness. She was emotionally unstable and suspicious. The history, therefore, was not as accurate as desired. She had always considered herself well until the present illness which began 6 years before admission to the hospital. The subjective manifestations noted during the first 4 years of her illness were weakness, being suspicious of others, and intolerance to cold. These symptoms became more pronounced during the last 2 years and were accompanied by amenorrhea, shortness of breath upon exertion, thickness and soreness of tongue, anorexia alternating constipation and diarrhea which changed to continuous diarrhea for the last 2 months, loss of body weight, clumsiness, ataxia, paresthesia of the feet and fingers, increase of mental symptoms, dryness of skin, and a brownish dermatitis over dorsum of hands and feet which appeared upon exposure to sunlight. She had received some "liver capsules" and intramuscular injections of liver extract without improvement. The dietary history was unreliable.

She was a well developed and emaciated white woman of about the stated age who coöperated poorly and answered questions reluctantly. The significant objective manifestations were slowness of speech, huskiness of voice, puffiness of face, broadening of nose, thickness of lips, dryness and coarseness of hair which was sparse over the trunk and extremities, dryness and coarseness of skin, brownish dermatitis over dorsum of hands and forearms and over dorsum of feet except for areas across the feet covered by the straps of her shoes, moderately severe stomatitis, enlarged and inflamed tongue, cardiac rate of 70, arterial pressure of 105/75, hemoglobin 72%, erythrocytes 3.0 million, leukocytes 4600, achlorhydria, occult blood in 7 of 9 stool examinations, and a basal oxygen consumption of 32% below normal. Stool examinations both direct and cultural revealed no pathogenic organisms. Blood agglutination reactions were negative for typhoid, paratyphoid, melitensis, and dysentery bacilli.

Course. In this patient the order of the specific therapy was the reverse of that of the previous case, and was concerned with the control of the pellagra through the administration of a high-caloric and high-vitamin diet with added vitamin B. The stomatitis, dermatitis, and diarrhea subsided. The appetite, strength, and body weight increased during the 3 weeks of this régime, but the psychosis was unchanged. The myxedema was then controlled by the addition of desiccated thyroid gland. The basal oxygen consumption increased to 5% above normal after 3 weeks. Sweating returned, intolerance to cold disappeared, and the speech and strength improved remarkably, but she continued to be somewhat suspicious of others and emotionally unstable.

Comment. The myxedema preceded the pellagra by several years in both cases. Certain manifestations of the former disease may have facilitated the production of the latter. The psychic and gastro-enteric disturbances resulting from the myxedema undoubtedly were factors in the prevention of an adequate food intake in the 2 cases. Gastric dysfunction has been considered as an etiologic factor in pellagra.[3] The frequent occurrence of achlorhydria and the small amount of gastric secretion obtained in some cases are evidence for gastric dysfunction in myxedema. Furthermore, the absence of the intrinsic factor of Castle[1] in 1 of 2 cases of myxedema previously reported[2] shows that gastric dysfunction may occur.

The psychic, neurologic, gastro-enteric, and to a less extent, the dermatologic disturbances which may be present in a case of coexisting myxedema and pellagra may be attributed to either disease. The 2 cases here presented did not have any demonstrable neurologic lesions. The psychic disturbances in both cases antedated the other symptoms of pellagra by several years and were due to myxedema until the onset of pellagra when the psychosis became increased. Both diseases were apparently contributing factors in the mental condition of both patients at the time of admission to the hospital. It is impossible, however, from the data available to state which of the two diseases played the dominating rôle. The presence of psychosis does not appear to alter the prognosis in myxedema, whereas it does in pellagra. The response to therapy by the 2 patients indicate that the presence of mental changes produced by the coexistence of the two diseases does not necessarily signify a grave prognosis.

Diarrhea is common in both diseases, but in myxedema it usually alternates with constipation. The continuation of diarrhea in Case 1 after the thyroid deficiency had been controlled and its termination in Case 2 before the administration of desiccated thyroid gland signifies that pellagra was the etiologic factor in both instances.

Dermatitis may develop in myxedema and in both instances this possibility was considered. The skin lesions in 2 previous cases in which dermatitis was thought to be due to myxedema were generalized and were not aggravated by exposure to sunlight. The typical character, distribution, and response to therapy of the dermatitis present in the 2 cases of this report indicate that pellagra and not myxedema was the etiologic factor.

Stomatitis and glossitis are common in pellagra, whereas they do not occur in myxedema without a vitamin deficiency. The glossitis observed in 3 cases of myxedema previously reported[2] was attributed to a vitamin B deficiency and suggested that deficiency diseases may develop in myxedema.

The relation of thyroid therapy and of antipellagra treatment to the disappearance of manifestations of the two diseases in both cases are shown in Table 1.

TABLE 1.—SYMPTOMS BEFORE AND AFTER TREATMENT.

	CASE 1.			CASE 2.		
	Before Rx.	After thyroid.	After anti-pellagra Rx.	Before Rx.	After anti-pellagra Rx.	After thyroid.
Intolerance to cold	+	0	0	+	+	0
Absence of sweating	+	0	0	+	+	0
Dryness of skin	+	0	0	+	+	0
Loss of hair	+	+	+	+	+	+
Slowness of speech	+	0	0	+	+	0
Huskiness of voice	+	0	0	+	+	0
Stomatitis	+	+	0	+	0	0
Dermatitis	+	+	0	+	0	0
Diarrhea	+	+	0	+	0	0
Paresthesia	+	0	0	+	-	0
Psychosis	+	+	0	+	+	±
Anemia	+	+	..	+	+	
Achlorhydria	+	..	..	+		
BMR	−45	+1	−5	−32	−32	−3

The development of pellagra in cases of myxedema emphasizes that deficiency diseases are likely to develop in any chronic malady, particularly if there are long standing gastro-enteric or psychic derangements.

Summary. The coexistence of pellagra and myxedema have not been described previously. Two such cases are reported. A fatal termination is almost certain if both diseases are not recognized. The manifestations of the myxedema which may facilitate the production of pellagra are discussed. An attempt was made in the 2 cases to ascertain which disease was responsible for production of manifestations which may be common to both maladies.

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THE SPECTROGRAPHIC DETERMINATION OF LEAD IN BLOOD FROM NORMAL HUMAN SUBJECTS.*

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It is of some general interest to know the distribution of a toxic substance such as lead in a population relatively unexposed to the metal as an industrial hazard.

Clear-cut data regarding the normal distribution of lead in the blood are exceedingly hard to secure. Most cases in which such information is sought have been suspected of plumbism or have had a definite history of exposure to the metal. It occurred to us that a class of first year medical students, selected from all parts of the country, would be excellent material for such a study. Consequently, we examined blood samples from the first year medical students in the entering class of 1936. Inquiry revealed that for the most part the subjects were free from definite exposure to lead. Some 12 or so gave a history of recent but casual contact with a possible source of the metal. None of the members of the series was employed in an industry or private pursuit known to be hazardous from the standpoint of lead intoxication within the last year.

One difficulty with such a group is the great preponderance of males. In our series, for example, there were 83 males and 6 females. But a similar sex ratio might be expected from the average group of workers in industry, so that for purposes of comparison our series is not without direct value.

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* Aided by grants from the Rockefeller Foundation, The Josiah Macy, Jr., Foundation, The American Medical Association and The National Research Council.

Method. Spectra of blood samples were obtained with an interrupted arc. The electrodes used were carbon rods especially purified for spectrographic analyses. As an added precaution each electrode was pre-heated to white heat in an oxygen-gas flame. Rarely if ever was difficulty encountered with contaminants in the electrodes after such treatment.

Blood samples were drawn into pyrex test tubes which had been cleaned finally in pyrex glass-distilled nitric acid. The tubes were stoppered with corks covered with a good grade of waxed paper to exclude dust and prevent contamination. After the blood had clotted, small pieces of the clot were placed on the ends of the electrodes and dried with moderate heat. The residue was excited in an interrupted arc. Since 100 flashes consumed nearly all the material on the electrode, it was necessary to prepare 3 separate samples. With the flashes occurring at 80 per minute, 300 flashes gave the required exposure. A Bausch and Lomb medium quartz spectrograph with a slit width of 0.015 mm. was used. Eastman 50 plates were employed throughout and gave uniformly good results.

Since these studies were made, we have found that a more uniform coating of the electrode can be had if the blood is first whipped with a motor driven stirrer until the clot is finely divided. A complete description of the apparatus for arcing the material has been described by McMillen and Scott.[4a,b] The instrument used in the present study differs slightly from that described in the above article in that the end rather than the side of the cylindrical electrode was covered with the sample. Also the electrode was held vertical and its position changed by hand.

Measurements of the lead content of the blood samples were made on the 2833.07 Å arc line.[6] This line was selected in preference to other of the sensitive lines because of its freedom from coincident lines. A study of the spectral tables shows that the only possible coincident line for the 2833.07 Å lead line is the 2833.2 Å iridium line. However, the absence of iridium in the sample was guaranteed, by the absence of the nearby 2836.4 Å line of iridium.

Estimates of the lead content of fluids may be made directly from density measurements of the photographed lead line. However, this method is subject to relatively large errors, of which the principle ones are those resulting from irregularities in the amount of the sample burned. To eliminate this source of error a method was adopted which relies on an internal standard. The density of an iron line near the 2833.07 Å lead line was used as a reference and all measurements on lead were made relative to iron. Iron was selected because it is recognized that the amount of this element in normal blood is relatively constant. In any event it does not fluctuate by factors of 10 or 100 as does lead. The reference line in these studies was the 2831.56Å iron line. It was not only conveniently close to the lead line under observation but it also had a comparable density. For normal blood the lead line was less intense than the iron but for definite cases of lead poisoning, the situation was reversed.

The factors leading to errors when line densities are taken as a measure of lead content of blood are apparent from an examination of the following relationship:

$$D_{Pb} \gamma (\log F_{Pb} + \log K_{Pb} + \log M) + \tau$$

where *D* is the line density, *F* the fraction of lead, by weight, in the sample. In the first place variables γ and τ are related only to the photographic process and may be regarded as constant when care is taken to assure uniformity in the developing process. The term involving *K* represents those factors which depend only upon the chemical and physical properties of the sample. The factors which pertain to the arcing process, *i. e.*, exposure time and amount of material consumed, are taken care of by the expression containing M. By introducing the reference line, M can be eliminated giving the following:

$$D_{Fe} - D_{Pb} = \gamma \log F_{Fe}/F_{Pb} + \gamma \log K_{Fe}/K_{Pb}$$

Since K can be assumed to be constant from sample to sample and is kept constant by careful developing of the plates, the difference in density may be considered to be *directly proportional to the logarithm of the ratio of the lead to the iron content.*

For the estimation of the proportion of lead found in the series of human blood samples, a standard set of rabbit bloods, to which known amounts of the metal had been added, were arced. This standard series was prepared to give concentrations from 0.005 to 1.0 mg. % of lead. The mean density difference of four exposures per sample was determined. These data were obtained by measuring directly the photographic tracing from a recording microphotometer (Fig. 1). A straight line was drawn through the density differences when these were plotted against the log of the lead concentration. With the aid of this mastergraph and the density differences of the normal samples, the lead content of these was determined.

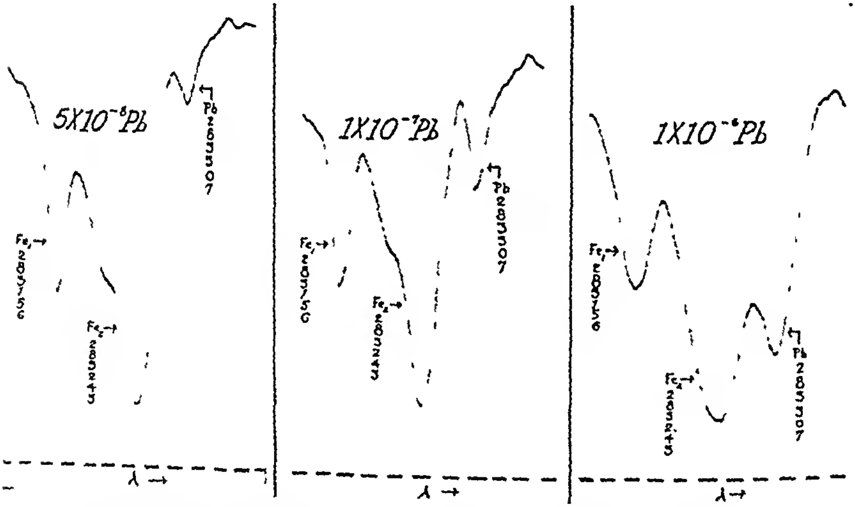

FIG. 1.—Recording microphotometer tracings of 3 leaded blood samples. A comparison of the distances of the peak for the lead line (at the extreme right of each tracing) from the dotted base line shows increasing density in the lead lines of the samples from left to right. Note the comparative equality in the level of the Feline 2831.56Å. This line was used as the internal standard for lead determinations.

Results and Discussion. In the present series, 44 blood samples failed to show traces of lead in quantities of 0.001 mg. or more per 100 cc. This figure represents the positive limit of the sensitivity of the method used without any preliminary concentration of the sample. It was felt that an extension of the procedure by attempting to concentrate the lead was disadvantageous because it not only lengthened the process but also introduced the possibility of contamination.

In the analysis of the data it was of considerable comfort to us to find about one-half (44) of our samples lead free. We interpreted this to mean that our method of blood collection was such that certainly constant, and perhaps occasional, contamination of the bloods was ruled out. It is almost axiomatic that with spectrographic studies a thorough scrutiny for all possible sources of lead contamination be given. An example of this type of contamination would be that of the solder joints in the needle used in withdrawing the sample.

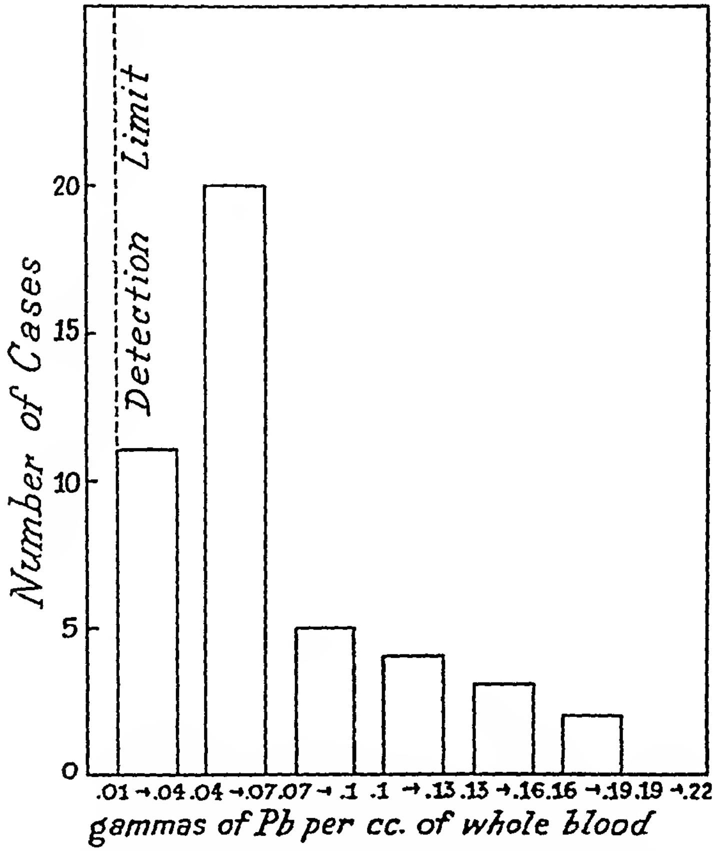

FIG. 2.—A simple graph of the distribution of lead in the 45 blood samples which showed the metal. The 44 samples which showed no lead would fall to the left of the line marked *detection limit* if the distribution graph were complete.

The next group of samples (Fig. 2) have been classed as those which contained from 0.001 to 0.009 mg. % of whole blood. In this category the bulk of the 45 lead containing bloods is to be found. Some 36 of the samples fell within this range. The modal lead content of the group was 0.004 mg. %. The distribution of this group is not symmetrical about the mean. This can be accounted for by the fact that our series had an insufficient number of cases to expect symmetrical distribution.

The remainder of the bloods, 9 in number, contain from 0.01 to 0.06 mg. % of lead. Six of these are grouped at 0.02 and 0.03 mg. %, 2 at 0.06 and 1 at 0.01 mg %. These cases with the greatest lead content of any of the series presented no symptoms, however vague, of lead poisoning. Careful questioning brought out in one case only a single clue as to the possible source of the metal. This particular person had sprayed a rose garden with lead arsenate mixture a number of times during the summer. His blood, however, contained only 0.01 mg. % of lead. The others in this group could give no suggestive answers to a large number of—to them inane—questions regarding eating, drinking, smoking and other personal habits.

The category of leaded bloods described above is of particular significance when considered in the light of the chemical findings of Litzner and Weyrauch[3] and Schmidt and Weyrauch.[5] These authors give a list of 34 cases in which the blood lead was found to range between 0.01 and 0.03 mg. %. In many of their cases the "subjektive Beschwerden" are suggestive. Even more so are their cases, 39 in number, in which from 0.03 to 0.06 mg. % of lead was found. In general, their results indicate that lead up to 0.02 mg. % may be expected in the normal and over 0.06 mg. % clinical symptoms of lead poisoning were usually found. In the present series it would seem that, with the single exception noted above, it is possible to have lead in the blood 0.0 up to 0.06 mg. % without history of lead exposure. Kehoe, Thamann and Cholak[2] report essentially the same findings for their series of 32 normal, nonindustrialized Mexicans, if one discounts, as they indicate should be done, 2 cases in which the lead content of the blood was as high as 0.07 to 0.08 and 0.25 mg. %.

Spectrographic studies of pathologic amounts of lead in the blood by Blumberg and Scott[1] indicate that the pathologic range is from 0.2 to 1.0 mg. %. Our experience with abnormal amounts of lead in human blood is in complete accord with this finding. For example, a case of plumbism contracted from polluted cistern water showed 0.32 mg. % of lead.

Summary. The spectrographic methods outlined gave accurate results with the type of material studied if reasonable care was exercised. The failure to find lead in the blood in one-half of the members of the series strengthens belief in the validity of the technical procedures involved. From the findings it is reasonable to expect as much as 0.06 mg. % of lead in the blood of normal persons. While in the present series the number of females is admittedly small, no sex difference in blood lead was observed.

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THE ETIOLOGIC IMPORTANCE OF FATIGUE AND THE PROGNOSTIC SIGNIFICANCE OF MONOCYTOSIS IN NEUTROPENIA (AGRANULOCYTOSIS).

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The etiologic factors responsible for malignant neutropenia or agranulocytosis have been studied intensively and much knowledge has been acquired by recent work on drug therapy and the development of the disease. The pharmacologic compounds most commonly incriminated have been amidopyrine,[16] dinitrophenol,[7] arsphenamine,[15] gold salts,[6] and recently sulphanilamide.[33] Many other medications have been mentioned. The importance of these chemicals has been variously evaluated by different authors. Kracke and Parker[13] claim that all their cases have taken drugs containing the benzene ring prior to the clinical onset of the condition. This view has received important substantiation from Plum[19] who states that no new cases of agranulocytosis have been reported in his hospital in Copenhagen from the time amidopyrine had been found to be a factor in the causation of the disease to January, 1935, whereas previously such patients were relatively common. On the other hand, Jackson[11] has shown that in 44% of 27 cases no drug has ever been used. There have been many reports based on careful investigation which substantiate this observation—that a considerable number of cases of neutropenia occur in which drug therapy is not a factor. Moreover, in a great many cases, drugs like amidopyrine have been taken for a considerable time without apparent ill effects and then suddenly the patient develops the disease.[10,11] To state that the subject has become allergic is hardly in keeping with our usual conception of allergy and is not borne out by investigation.[9,27] Moreover, if this is a peculiar type of sensitivity like an Arthus phenomenon, the search for the factors which suddenly render the resistant patient susceptible is particularly important.

Because of the apparently explosive nature of neutropenia, the high fever and the angina, an infectious etiologic agent was diligently sought. In spite of much work[5] it is generally believed now that in most cases infection is the result rather than the cause of the granulocytopenia. This has been shown by patients who had daily blood counts for several months and in whom the neutrophil depression preceded the other symptoms and signs.[21b,22a] In a few cases the possibility of infection as one of the etiologic agents must be considered.

Menstruation is undoubtedly an important factor in this disease.[12 26 29] Many cyclical cases have been described in which this was the only etiologic condition and in which no drugs were known to have been used. One of my patients had an attack of agranulocytosis, sometimes mild and occasionally severe, every 28 days for 2 years without any use of drugs. These attacks ceased during pregnancy and after delivery never recurred. She has been free from attacks now for more than 6 years.

TABLE I.—ETIOLOGIC FACTORS IN NEUTROPENIA.

Patient.	Sex.	Fatigue.	Drugs.	Menstruation.	Infection.	Remarks.
C. N	[illegible]	+	−	+	+	4 attacks; 2 infected teeth removed after fourth attack; well since; received amidopyrine during fourth attack.
G. W	♀	+	+	−m	−	Dinitrophenol.
M. O'S	♀	+	?	+	+	No history of drugs as cause of attack elicited; midol taken after recovery, suffered chilliness.
F. H	♀	+	[illegible]	−m	?	Nembutal taken; difficult to determine if infection or neutropenia was primary.
L. W	♀	[illegible]	+	−m	?	Amidopyrine; history of fatigue not determinable.
R. McC.	♂	+	+	−	?	Salvarsan; lues.
E. S	♀	+	+	+	−	Allonal.
W. Z	♂	+	+	−	+	Amidopyrine; clinical diagnosis; aplasia of bone-marrow or leukemia; autopsy diagnosis: chronic neutropenia.
H. H.	♂	[illegible]	+	−	+	Lues; neosalvarsan; chronic Vincent's angina; history of fatigue not determinable.
P. H.	♂	+	+	−	+	Amidopyrine, sinusitis.
G. B.	♀	+	+	−m	?	Allonal; difficult to determine if infection or neutropenia was primary.
S. W.	♀	+	?	−m	−	Roentgen ray therapy before attack; no history of drug elicited.
E. F.	♀	+	+	−m	+	Arthritis; chronic pharyngitis; amidopyrine.

m = passed menopause.

A careful study of patients' histories makes it evident that a great many cases are associated with fatigue. Sometimes the story dealt with excessive work and worry. Usually sleeplessness was present. Some of these patients took amidopyrine for this condition but many did not. In some reports it is difficult to determine whether the fatigue was not an evidence of the disease as in the chronic cases of agranulocytosis. But in many individuals long continued fatigue preceded acute attacks and in some, blood studies showed normal counts during the fatigued states which antedated the acute illness.

To determine the relative importance of the etiologic factors mentioned, 13 cases admitted to this hospital during the past 5 years were studied (Table 1).

It can be seen that fatigue previous to the onset of illness was found to be a prominent predisposing factor in 11 of the 13 patients.

In 2 cases (L. W. and H. H.) no inquiry was made as to this fact. Drugs were known to be of etiologic significance in 9 cases, amidopyrine in 6, arsphenamine in 2, and dinitrophenol in 1. In the remaining 4 cases no evidence of drug administration could be elicited. One patient (S. W.) was subjected to Roentgen ray treatment. One patient (G. N.) not only was observed through 4 attacks and known never to have taken drugs previous to the onset of the illness, but during one of her attacks received 1.62 gm. of amidopyrine as a sedative and recovered. Menstruation was a factor in 3 of the 9 female patients; 6 had passed the menopause. Infection was of possible etiologic importance in 6 patients; in 4 no history of infections could be elicited, and in 3 no previous infection was found.

An analysis of some of these cases emphasizes the importance of fatigue as a precursor to neutropenia when this factor is considered. Patient G. N. had 4 attacks. She volunteered the information that she was extremely fatigued and worried about her business before the first and third attacks. Before the fourth attack she was unable to sleep for 3 nights and was exhausted by financial and family problems. The chief therapeutie measures in her case were the removal of 2 infected teeth and the readjustment of her activities and responsibilities so that most of her worries and fatiguing duties were removed. She has had no further trouble since September, 1932. She had never taken drugs.

Patient G. W., who had taken dinitrophenol, stated that for weeks before her illness she was engaged in "hectic social life," having very little time for sleep or rest.

Patient M. O. S. took no drugs. She worked 12 hours a day at an Art Theatre, ate irregularly, and had become progressively more fatigued for a year. Her attack coincided with her menstrual period. Eleven months after her recovery she was readmitted for dilatation of her sphincter and repair of an anal fissure. She had taken Midol and in spite of having noticed a chilly sensation, her blood count showed 11,300 W.B.C. and 68% polys.

Patient F. H. complained of sleeplessness for 5 nights. The only drug she received was sodium pentobarbital after her angina was present and her throat was painted with neoarsphenamine.

Patient R. McC., who had been receiving salvarsan injections twice a week for 5 weeks, stated that his sleep was so disturbed that he was sure he averaged no more than an hour's sleep for several nights preceding his attack of agranulocytosis. "He reached a breaking point from fatigue" due to his lack of sleep, his work during the day, and studying law at night.

Patient E. S. took allonal tablets for years with no apparent ill effects. She wrote a Broadway success and came East to rehearse it. She spent 18 hours a day in intensive work, could not sleep at night and was utterly exhausted at her menstrual period which coincided with her fatal attack.

Patient W. Z. was a physician who took amidopyrine occasionally. During the 2 weeks he was working day and night and was exhausted when he developed a sore throat.

Patient P. H. had a cold and could not sleep for a few days before the onset of his illness. He was exhausted and took 2 amidopyrine tablets.

Patient G. B. was always a very poor sleeper. She had been taking allonal every night for almost 3 years. For a few weeks before her attack she had been taking care of a grandchild and was utterly exhausted.

Patient S. W. was suffering from pruritus of such intensity that she could not sleep. She had also received Roentgen ray therapy for the local condition.

Patient E. F. was an elderly lady who had many responsibilities as a business manager. For one year she had felt fatigued, had arthritis and sore throats, and took amidopyrine occasionally. One day before her acute illness she was very tired but entertained some friends until late at night.

A most illuminating illustration of the importance of fatigue in neutropenia is afforded by the case record of a physician, J. J., not included in the table, who was seen after his fourth attack. He gave no history of drugs but each attack coincided with a period when he had many sleepless nights due to a concentration of obstetrical cases. His second attack was characterized by a severe submaxillary induration which necessitated the insertion of a permanent tracheotomy tube. When seen on October 13, 1933, he stated that he was very tired due to several obstetrical cases within a week, that he had little sleep for 3 or 4 nights, that he had a few more patients to deliver, and then he would take a vacation. He was so impressed with the relation of fatigue to his attacks that he planned to give up his general practice and devote himself to some less strenuous field in medicine. His W.B.C. count was 3600 and he had 37% neutrophils. The next notice of this physician appeared in the obituary column of the *Journal of the American Medical Association* of December 9, 1933, stating that his death occurred from agranulocytosis and bronchopneumonia on November 17. This fatal fifth attack was certainly associated with fatigue and might even be considered an "obstetrical death."

A perusal of the literature indicates many cases of agranulocytosis in which fatigue, worry, and sleeplessness were sufficiently marked to call the attention of the physician to this factor. In some of these, drugs are considered the most important etiologic agent; in others no evidence of drugs is found. Some of the workers who emphasized fatigue are Scanlan,[24] Reed,[20] Briscoe,[3] Roberts and Kracke,[22b] Beck,[1] Martin,[18] Hall,[8] Suzman,[28] Walker,[30] Davis,[4] Wilson,[31] Israëls and Wilkinson,[10] Klumpp,[14] von Bonsdorff,[2] and Magee.[17]

The importance of predisposing factors in addition to or other than drugs, as exemplified by fatigue, is suggested by studies on the use of amidopyrine in a large series of cases with no change in leukocyte or granulocyte counts.[25]

Table 2 presents the *relationship* of prognosis to the *monocyte* response as seen in sequential counts. Of the 13 patients, 9 recovered and all had sustained relative and, in most cases, absolute monocytosis. Moreover, in many of the patients an increase of monocytes preceded the return of neutrophils, the rise in leukocyte count, the drop of temperature or symptomatic improvement. Of the 4 fatal cases, 2 showed a progressive decrease in monocytes and 1 was reported to have had an increase from 0 to 20% just before death as judged by a house officer's estimate of a smear taken 5 minutes before death. The fourth patient had an atypical case diagnosed clinically as aplasia of the bone marrow or acute leukemia and chronic neutropenia at autopsy. Two days before death a count of 30% monocytes was reported. The patients who recovered had monocyte peaks ranging from 17 to 66% and in all cases the monocytosis was sustained for several days.

TABLE 2.—RELATIONSHIP OF MONOCYTE RESPONSE TO PROGNOSIS IN NEUTROPENIA.

Patient.	Monocytes on sequential counts (per cent).	*Termination of illness.*	Remarks.
C. N.	1st attack 47 (reported)	Recovery	
	2d attack 17	Recovery	
	3d attack 15, 11, 26, 23,* 15, 11, 9	Recovery	*Distinct improvement.
	4th attack 15, 11, 26, 23,* 15, 11, 15	Recovery	*Distinct improvement.
G. W.	32, 46,* 41, 22, 13	Recovery	*Distinct improvement.
M. O'S.	28, 30,* 23, 16, 13, 7, 8	Recovery	*Distinct improvement.
F. H.	26, 20,* 10, 12, 8	Recovery	*Distinct improvement.
L. W.	0, 20 (see remarks)	Died	Intern's estimate of smear taken 5 minutes before death.
H. McC.	54, 36, 22,* 14, 14, 9	Recovery	*Distinct improvement.
E. S.	0, 9, 1	Died	
W. Z.	0, 0, 0, 6, 13, 6, 30	Died	Clinical diagnosis: aplasia of bone-marrow or leukemia; autopsy diagnosis: chronic neutropenia.
H. H.	31, 40, 53, 65, 55, 37, 10,* 18, 16, 12, 19, 10, 12	Recovery	*Distinct improvement.
P. H.	45, 66, 26,* 24, 21, 23, 21, 10, 5, 1	Recovery	*Distinct improvement.
G. B.	9, 6, 22, 15,* 18, 17, 16, 16, 14, 11, 6, 9	Recovery	*Distinct improvement.
S. W.	10, 5	Died	Roentgen ray therapy before attack.
E. F.	1, 2, 5, 3, 3, 2, 8, 10, 15, 11,* 10, 16, 18, 12, 9, 7, 10, 8, 12	Recovery	*Distinct improvement.

The importance of *monocyte* increase as a favorable prognostic sign has been shown previously in infections[21] and in neutropenia in particular by Rosenthal and Abel.[23] Wolff's[22] case is significant. A child was almost moribund 17 days after the onset of illness. Then the monocyte count rose to 28% and then to 57% with rapid recovery following. Briscoe's[3] patient illustrates the rise of monocytes before return of neutrophils in a favorable case. In spite of occasional reports like one of Hall's,[8b] in which a fatal outcome resulted in spite of a monocyte count of 30% and subsequently of 45% it is generally found that monocytosis points to recovery.

Comment. In a disease like malignant neutropenia it is difficult to assess the relative importance of each etiologic factor in every case. Certainly drugs like amidopyrine merit careful consideration. And still individuals do not take such a medication when they are perfectly normal. Moreover, even those "sensitive" subjects who are given this analgesic experimentally and show a depression of neutrophils rarely develop the characteristic signs and symptoms of the condition. They may present mild evidences of malaise but it is unusual to encounter severe illness following such experiments in these persons who were in good condition when the drug was administered. From a practical standpoint it seems desirable to eliminate or modify all factors which may be of etiologic significance. To avoid a recurrence all patients who have recovered should be cautioned (*a*) to shun drugs known to depress the neutrophils; (*b*) to remove foci of infection if possible; (*c*) to reduce activities just before and during the menstrual period; and (*d*) to obtain adequate sleep and, as far as possible, guard against fatigue. The patients who have followed these rules have had no recurrences. The few patients who could not carry out all these suggestions found adequate sleep the most important single factor in their general improvement.

Conclusions. 1. Four factors were found to be of importance in causing neutropenia in 13 patients. These were (*a*) fatigue, (*b*) drugs, (*c*) menstruation, (*d*) infection.

2. In the cases reported in this study fatigue due to excessive work, lack of sleep, and worry was more frequently encountered than any of the other etiologic conditions.

3. Monocytosis is an evidence of good prognosis. To be significant it must occur early in recovery and persist.

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OPTIC ATROPHY IN PERNICIOUS ANEMIA.

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Other than the pathologic changes in the spinal cord, involvement of the central nervous system is rare in primary anemia. Mental symptoms occur at times, but generally are due to a severe grade of anemia, rather than actual organic change. Barrett,[1] however, described focal cortical lesions accounting for psychotic manifestations.

Visual disturbances in primary anemia have been recognized for many years. These have been caused by retinal hemorrhages, edema of the nerve head and retina, and thrombosis of retinal artery or vein.

Optic atrophy has been mentioned by a number of authors as of rare occurrence. Most material available on the subject is contained in textbooks. Brain,[3] only, described optic atrophy as occurring not uncommonly, stating that "bilateral primary optic atrophy is observed in 5% of cases." Osler[9] states that optic neuritis is rare. Dana[5] noted optic atrophy only once. Grinker[7] believes that such lesions occasionally result from degeneration of retinal cells because of ischemia.

Unquestionably it is true that optic atrophy may occur as the result of ischemia, as is substantiated by such occurrence at times after severe hemorrhage from peptic ulcer, at postpartum and from other causes. However, the matter of interest to the present discussion is atrophy obviously not of ischemic origin, but rather most probably due to intrinsic degenerative changes. Of especial importance is the fact that this neurologic manifestation may be the presenting symptom, just as combined sclerosis may make itself manifest before clinical symptoms referable to the anemia itself.

Dereux[6] described a patient with optic atrophy and pernicious anemia whose vision did not improve after treatment with liver. He also noted that cranial nerve involvement in pernicious anemia is very rare. Recently Cohen[4] reported 2 cases in which visual impairment was the presenting symptom. This report led Box[2] to record a similar case in the same journal some months later. Other than this we have been unable to find similar case reports in the literature.

Woods and Rowland[10] in a careful study of 201 patients with disease of the optic nerve found 11 in whom the etiology could not be established, but pernicious anemia was not mentioned among the possible causes. Jelliffe[8] in a very comprehensive treatise on the optic nerve and its disorders failed to mention pernicious anemia as a factor in his discussion.

Case Reports. CASE 1.*—O. M., a white male, aged 56, foreman of a road-grading gang, entered the Medical Out-patient Department of the University of Michigan Hospital on April 8, 1927. He complained of impaired vision, weakness, and numbness of the extremities. In July, 1926, the patient began to note impairment of his vision. He found that he made mistakes in reading numbers on a measuring tape used in road grading, and, as a result of these inaccuracies, was forced to quit work in October, 1926. The visual impairment was progressive at first, but had been stationary from October to the date of admission. It was impossible to read print at the time of entering the clinic. About January 1, 1927, the patient began to notice coldness of the feet and legs. Numbness accompanied this. The symptoms progressed so that upon admission he complained of coldness and numbness up to the waist. Within the preceding month he had noted stiffness of the knees while walking. The soles of the feet gave the impression as if he were "walking on cushions." There had been no loss of weight. Memory was good. There had been no bladder disturbance, shooting pains, girdle sensations nor difficulty in walking in the dark. Soreness of the tongue had not been noted. The appetite had been good. In the past history nothing of significance was found, except that a year before the patient had had a weak spell and had fainted, at which time a physician prescribed digitalis. Venereal disease was denied. The patient had been a moderately heavy smoker. He was a heavy drinker of spiritous liquors before prohibition, but since then he used only home-made beer.

Physical Examination. He was a large, fairly well nourished male. The hair was gray. The skin showed slight pallor. Pupils were contracted and unequal, the right being larger than the left; they did not react to light, but did react for accommodation. The edges of the tongue were slightly atrophic. The peripheral arteries were thickened and the brachial arteries were tortuous. The heart was normal in size, rate was 80, blood pressure 125 systolic and 80 diastolic. A systolic murmur was heard over the precordium. The aortic second sound was accentuated. The lungs and abdomen were negative. Liver and spleen were not palpable. Neurologic examination, checked by a neurologist, showed the presence of biceps, triceps and knee reflexes. The left tendo-Achilles reflex was absent, the right was diminished. Sense of position of the toes was present. Vibratory sense was lost over the left ankle. Ataxic gait was present, worse with the eyes closed. Fundus examination, checked by an ophthalmologist, showed pallor of both disks, the left showing unquestioned atrophy. At this point the tentative diagnosis was tabes dorsalis.

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* Cases 1 and 3 were studied by one of us (R. H. K.) in the Department of Medicine, under the Directorship of Dr. J. D. Bruce, at the University of Michigan Hospital, Ann Arbor, Mich.

Laboratory Data. The urine was negative. Blood Wassermann test was negative. The spinal fluid was clear, contained 9 cells per c.mm., no globulin, and a negative Wassermann and gold sol. On April 14, 1927, the hemoglobin was 54% (Sahli), red blood cell count 1,800,000, and white cell count 5900. The differential count was: neutrophils, 57%; lymphocytes, 37%; monocytes, 2%; and eosinophils, 4%. Red cells showed slight poikilocytosis, anisocytosis, polychromatophilia and macrocytosis. Reticulocytes were present to 1%. The blood bilirubin was 1.5 mg. %. Achlorhydria was present.

Course. The patient was placed on high liver diet (500 gm. daily) on April 15, 1927. He was discharged from the hospital on June 1, 1927. He was given hydrochloric acid with the diet. The blood picture improved so that by April 26, the hemoglobin was 60% (Sahli), the red blood cells numbered 2,040,000 with 14% reticulocytes. Improvement was progressive and by July 1, 1927, the hemoglobin was 83% (Sahli) and red blood cell count 4,830,000. As the blood improved the gastro-intestinal symptoms disappeared and subjectively the numbness improved. Vision remained unchanged.

Case 2.—T. S., a white man, aged 59, entered the Out-patient Department of Vanderbilt University Hospital on May 12, 1936. His complaint was weakness which had been gradually progressive for 6 months following "influenza." A month after the onset of his weakness he noticed difficulty in reading newspaper print. This visual defect progressed until at the time of admission he could only distinguish large objects at short distances. Throughout his illness he has had more or less generalized soreness of his muscles. He said that while his legs and arms felt "dead," they were also tender to touch. His tongue had not been sore nor had he had any diarrhea. He had lost about 16 pounds during his illness, his weight at time of admission being 106 pounds. The past history was of no apparent significance except that all his teeth had been removed 3 years before, and he had obtained no dentures.

Physical Examination. The patient was found to be a small, poorly nourished man, appearing chronically ill. There was diffuse brown pigmentation of his face and arms, about the axillary folds, patches of similar pigmentation inside the right cheek. There was generalized muscle weakness. The pupils reacted normally to light and accommodation, and were equal and regular in outline. The ophthalmologist reported visual acuity of 5/200 for the right eye and 10/200 for the left eye. Though the patient was somewhat uncoöperative, the visual fields showed no apparent gross defect. The fundi were described as being pale in reflex and the optic disks pale with pronounced temporal pallor. The impression was optic atrophy of unknown etiology. The heart and lungs were not remarkable. There was slight tenderness just beneath the right costal margin, but nothing abnormal was felt there. The liver and spleen were not palpable. There was a hydrocele of the tunica vaginalis on the left. The knee and ankle jerks were absent. He walked with a wide base and showed a positive Romberg test. Vibratory and position senses were lost in both lower extremities. The abdominal, cremasteric, biceps and triceps reflexes were present but sluggish. A tentative diagnosis of tabes dorsalis was made and the patient was admitted to the hospital.

Laboratory Data. Red blood cell count was 1,350,000 with 5 gm. of hemoglobin. The white blood cell count was 2200 (neutrophils, 41%; eosinophils, 1%, lymphocytes, 43%; and monocytes, 15%). The smear was typical of pernicious anemia. Gastric analysis showed no free hydrochloric acid even after histamine. His spinal fluid was clear, showed no increase in pressure, no cells, a negative Pandy test and a negative Wassermann test with a flat colloidal mastic curve. The urine showed nothing abnormal. Four stool specimens were negative for parasites, ova and occult blood.

Clinical Course. The patient was given 6 cc. of Lilly's concentrated liver extract intramuscularly daily for 4 days and then at decreasing intervals. From an initial level of 0.25%, the reticulocytes increased to 42% 6 days after beginning specific treatment. This was followed by a rise in red cells and hemoglobin to 3,750,000 and 11 gm. respectively, 19 days after the beginning of liver therapy, at which time he was discharged from the hospital. There was marked subjective improvement both in strength and vision. However, tests of visual acuity made approximately 3 months after the first tests showed values of 2/200 for the right eye and 10/200 for the left eye. The fundi and nerve heads appeared as on the first examination, as did the visual fields. Six months after admission to the hospital, the red blood cell count was 5,200,000 with 16.5 gm. of hemoglobin. He had been receiving liver extract regularly at weekly intervals during this time. There had been a gain of 6 pounds in weight. Newspaper headlines were now visible for the first time since the period of observation began. Ten months after admission to the hospital his visual acuity was 20/200 for the right eye and 20/200 for the left eye.

CASE 3—N. W., a white male, aged 50, boiler-maker by occupation, entered the Medical Service of the University of Michigan Hospital on November 17, 1925. His complaints were weakness and shortness of breath, which began 6 months before. Because of weakness he gave up work for 3 months, then regaining strength, he again worked until 12 days before admission to the hospital. He noted a burning sensation of the tongue. Numbness and coldness of the feet were present at the onset of the illness. These symptoms improved, but the abnormal sensation was felt in other parts of the body. Later the feet became so tender he could not walk. Ataxia developed. Vision had become progressively worse since the onset of the present illness. There was nothing of significance in the past history. The patient did not use alcohol. The wife and 6 children were living and well.

Physical Examination. Only important points in the examination are mentioned. The patient presented a marked pallor with a yellow tint. Pupils were irregular and failed to react to light. The tongue showed atrophy of the papillæ. Deep reflexes were normal. The ophthalmologist reported bilateral optic atrophy.

Laboratory Data. Blood Wassermann test was negative. On admission to the ward, the blood showed a hemoglobin of 22% (Sahli), red blood cell count of 820,000 and white cell count of 3200. The red cells presented anisocytosis and poikilocytosis.

Clinical Course. During the course in the hospital, the patient received 10 blood transfusions. At no time did the hemoglobin or red cell count rise above 31% and 2,600,000 respectively. The blood values steadily decreased from the high point. Edema, hydrothorax and ascites developed, and the patient died 4 months after admission. Permission for autopsy was not obtained.

Comment. Three cases of primary anemia have been presented in which visual impairment was prominent. In the first case, it was the presenting symptom and only symptom for 6 months, and on the first examination the patient had an anemia not severe enough to account for the changes on the basis of ischemia. Because he was seen during the prohibition era when methyl alcohol poisoning was not uncommon, this phase of the history was carefully considered. In the second case, the visual disturbance appeared early among the symptoms and again at a time when the degree of anemia could not account for the optic lesion.

The third case was included in this report because optic atrophy was present in a patient who undoubtedly had primary anemia. Study was incomplete in that no spinal fluid examination was included. This patient had an anemia of such grade upon admission that question might arise as to the part played by ischemia in the production of optic atrophy. However, visual symptoms had steadily progressed from the onset of symptoms and during a probable remission.

Especially worthy of emphasis are the diagnostic aspects of such cases. In the first 2 cases the early tentative diagnosis was tabes dorsalis.

Discussion. Since visual disturbance is not generally included as one of the usual symptoms of pernicious anemia, it seems worth while to call attention to this possibility. Especially is this of value since if such a condition is considered, treatment instituted sufficiently early may stop the progressive degeneration. Further, it brings out the fact that clinicians must be aware constantly of unusual possibilities, since the diagnosis of tabes dorsalis was initially made in the first 2 of the reported cases, because of attendant findings in addition to optic nerve changes.

The incidence of optic atrophy in cases of pernicious anemia may be gauged to some degree by analysis of case groups. During an 11-year period at Vanderbilt University Hospital, there were 69 cases of pernicious anemia. Of these, 74% were found to have symptoms or signs of central nervous system involvement. In a 5-year period preceding the admission of Case 1, 164 acceptable cases of pernicious anemia were admitted to the University of Michigan Hospital. Fifty-five per cent of these patients presented subjective or objective evidence of central nervous system changes. During the admission of the total of 233 cases to their respective hospitals there were 3 patients who suffered from optic atrophy.

As noted above, optic atrophy is occasionally known to follow severe sudden hemorrhage. It has been said that ischemia may account for optic nerve changes in pernicious anemia, but it seems to us that this belief is open to question. The sudden depletion of blood seems to be of more importance in optic atrophy due to hemorrhage than the degree of anemia. It is not infrequent to see patients with pernicious anemia having a hemoglobin of 4 to 5 gm. and a red blood cell count of 1,000,000 or less; yet optic atrophy is certainly rare in these cases, whereas in sudden hemorrhage the hemoglobin and red cell count rarely are depressed to like degree. Patients with pernicious anemia notoriously adapt themselves well to a high degree of anemia in contrast to those with anemia, usually of less degree, from other causes.

In the patients reported in this paper, 2 had blood counts and hemoglobin values not low enough to indicate that ischemia was the factor in their optic atrophy, and nothing in the history indicated that anemia had been more severe at any time for symptoms had been progressive. The third case, though he presented a low red blood cell count and hemoglobin content, had had visual symptoms from the onset of his complaints, which seems to indicate that optic nerve disease was progressive, independent of the degree of anemia.

Summary. 1. Three cases of pernicious anemia with optic atrophy are presented.

2. The infrequency of this complication has been discussed in light of a relatively high percentage of cases showing evidence of spinal cord disease.

3. It seems to us that optic atrophy when it occurs in pernicious anemia is an intrinsic degenerative process rather than due to ischemia itself.

4. That optic atrophy may be prominent in the clinical picture of pernicious anemia, and that it may even be the presenting symptom, is emphasized.

5. It is of interest that the tentative diagnosis of tabes dorsalis was made in 2 of the 3 cases reported.

6. The early recognition of visual disturbances on the basis of pernicious anemia is essential to the preservation and possible restoration of vision.

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THE COURSE OF HYPERTENSIVE HEART DISEASE.

IN RELATION TO GROSS ARTERIOSCLEROSIS.

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IN a previous study on the etiology of organic heart disease[6a] it was stated that arterial hypertension appeared to have no relation to gross arteriosclerosis; further, that these hypertensive patients with gross arteriosclerosis have outlived the damaging effects of their hypertension and have reached the stage where they developed the *arteriosclerosis.* This *arteriosclerotic-hypertensive cardiac* group ranks third in importance in the etiology of organic heart disease, affecting 11% of cardiac sufferers.[6a]

Apparently the original statement on this relationship was made by Lee[7] who reported that 69% of his 53 cases of hypertension had arteriosclerosis. This view was modified by O'Hare and Walker,[9] who stated that undoubtedly many cases of essential hypertension which are said to be free from association with arteriosclerosis, in reality may have a considerable degree of sclerosis of the small vessels. In spite of the anatomic findings of arteriosclerosis in the terminal arterioles of his 72 cases, Fishberg[3] offered a different opinion. He held the view as untenable that hypertension is due to the statically increased resistance offered by the organic lesions of the arterioles and that a true generalized arteriosclerosis does not exist in association with essential hypertension, and, therefore cannot be considered the cause of the latter. He added that changes in the arterioles of a nature similar to the arteriosclerosis of essential hypertension occurs physiologically with advancing years.

In an analysis of 500 cases of arterial hypertension Nuzum and Elliott[8] found no relation between arteriosclerosis of the larger vessels and hypertension. Rosenthal,[11] after a very extensive study on atherosclerosis, stated that arterial tension as determined by the weight of the heart was an important factor in the production of atherosclerosis, *but* that atherosclerosis and hypertension are not synonymous. In 48% of his cases atherosclerosis occurred without hypertension. Bell and Clawson,[2] however, from an autopsy study of 420 cases of essential hypertension, concluded that it was incorrect to state that "arteriosclerosis has no connection with hypertension."

The present clinical study of 127 patients with gross arteriosclerosis and hypertensive heart disease was analyzed with these diverse views in mind. The average known duration of the high blood pressure was 12 years for the entire group, but varied from a known duration of 3 to 22 years. The criteria followed for the diagnosis were those suggested by the American Heart Association.[5]

The highest incidence of these combined conditions fell in the seventh decade, 61.4% (Table 1). The common decade for the non-arteriosclerotic hypertensives is the sixth, 49.7%, with 78.8% occurring in the 40-to-60 year period, the "hypertensive age."

TABLE I.—PERCENTAGE IN THE AGE GROUPS.

Ages.	Male.	Female.	Total	%.
51 to 60	18	2	20	15.7
61 to 70	70	8	78	61.4
71 to 80	23	4	27	21.3
81 to 86	2	0	2	1.6
Totals	113 (89%)	14 (11%)	127 (100%)	100

Many of the arteriosclerotic patients in this study (21.3%) first learned of their high blood pressure in the sixth decade, but reached the eighth decade before the break in cardiac compensation occurred.

The duration of the disease from the onset of the first cardiac symptom, dyspnea of the persistent type most often, was estimated in the 46 known deceased patients (Table 2). The data on the 81 living patients was also studied in order to compare the duration in both groups of patients. Of the deceased patients, 80.4% died within 2 years after the onset of cardiac symptoms. The percentage of patients still living who were observed within 2 years after the onset of symptoms was 76.5%, approximately the same ratio.

TABLE 2—DURATION OF DISEASE AFTER ONSET OF CARDIAC SYMPTOMS.

	Deceased.				Living.			
Duration	M.	F.	T.	%	M.	F.	T.	%.
1 day to 6 months	24	2	26	56 5	33	5	38	46 9
7 months to 1 year	6	1	7	15 1	11	0	11	13 5
2 to 5 years	8	1	9	19 6	24	2	26	32 2
6 to 10 years	2	1	3	6 5	4	1	5	6 2
11 to 20 years	0	1	1	2 3	1	0	1	1 2
Totals	40	6	46	100 0	73	8	81	100 0
	(37% deceased)				(63% living)			

After the appearance of congestive heart failure the duration of life in these arteriosclerotic-hypertensives was short. Of the deceased patients, 77.0% died within 6 months after the occurrence of congestive failure (Table 3).

TABLE 3.—DURATION OF DISEASE AFTER ONSET OF CONGESTIVE HEART FAILURE.

	Deceased				Living			
Duration	M	F.	T.	%	M.	F	T.	%
1 day to 6 months	30	4	34	77 0	48	6	54	67 5
7 months to 1 year	3	2	5	11 1	14	0	14	17 5
2 to 5 years	4	0	4	9 8	10	2	12	15 0
6 to 10 years	1	0	1	2 1	0	0	0	0 0
Totals	38	6	44	100 0	72	8	80	100 0

TABLE 4—PERCENTAGE OF THE AGE GROUPS AT DEATH

Ages	Male	Female	Total	%
51 to 60	1	0	1	2 2
61 to 70	21	3	24	53 3
71 to 80	16	3	19	42 3
81 to 88	1	0	1	2 2
Totals	39	6	45	100 0

As to the age at death in these patients, Table 4, indicates the late age at which these patients died. There were 44.5% of the deceased over 70 at the time of death. Only 1 of the 20 patients who developed cardiac symptoms in the 51-to-60 age group died in that same age group. When this was compared with the non-arteriosclerotic hypertensive group,[6b] it was noted that 50.5% died in the same age group (51 to 60), and 30.2% died before they were 50 years.

The common cause of death was congestive heart failure (Table 5). Coronary occlusion was frequent as an additional factor in the 127 cases (Table 6), as it occurred in 9.5% of the patients. Positive blood Kahn tests were found in 7.0% of these white patients as compared with only 3.0% in the non-arteriosclerotic hypertensive white patients.[6b]

TABLE 5.—PERCENTAGE OF CAUSES OF DEATH IN 45 CASES.

Causes of death.	M.	F.	T.	%
1. Congestive heart failure	28	4	32	71.2
2. Cerebral hemorrhage	5	1	6	13.4
3. Coronary occlusion	3	0	3	6.6
4. Uremia	2	0	2	4.4
5. Spontaneous rupture of aorta	1	0	1	2.2
6. Mesenteric embolism	0	1	1	2.2
Totals	39	6	45	100.0

TABLE 6.—ADDITIONAL FACTORS IN THE 127 CASES.

Conditions.	M.	F.	T	%.
1. Coronary occlusion	11	1*	12	9.5
2. Positive blood Kahn tests	9	0	9	7.0
3. Cerebral hemorrhage	2	2	4	3.1
4. Diabetes mellitus	2	1*	3	2.3
5. Obesity	1	1	2	1.6
6. Cardiac aneurysm	1	0	1	0.7
7. Duodenal ulcer	1	0	1	0 7
8. Femoral embolism	1	0	1	0.7

* Same patient.

Three illustrative cases have been appended to indicate several interesting features in hypertensive patients who live long enough to develop gross arteriosclerosis.

Patient 1. C. P., a 71-year-old white male laborer, was a known hypertensive with a blood pressure around 220 systolic for the past 15 years. He first learned of his elevated blood pressure in January, 1917, at the age of 55. No symptoms or signs which are related to arterial hypertension occurred until February, 1931, when he began to have frequent nose-bleeds. In December, 1931, he became markedly short of breath and this led him to seek medical attention. In January, 1932, his blood pressure was 220 systolic and 130 diastolic and it remained at that level until his death in March, 1932. On February 1, 1932, an examination revealed dulness over both lungs posteriorly with crepitant râles at the bases. The transverse diameter of the heart was 17 cm. All palpable arteries were sclerotic and hopping in character. The liver was not enlarged and no edema was noted. Death resulted from a cerebral insult. An autopsy revealed multiple areas of encephalomalacia in the cortex of the right frontal and occipital lobes, right optic thalamus and the left internal capsule. There was a marked sclerosis of the basilar cerebral arteries, the coronary arteries, and the renal arteries. The heart weighed 410 gm. and was only moderately hypertrophied. He lived 15 years with high blood pressure after it was discovered.

but undoubtedly had the hypertension a much longer period of time. Death was due to encephalomalacia and not to cardiac failure, the dyspnea notwithstanding and in spite of the involvement of the coronary arteries.

Patient 2. S. K., a 75-year-old white male, in May, 1932, complained of severe substernal pain of 5 days' durations. Dyspnea had appeared at the same time and he was very weak. He stated that he first learned he had high blood pressure in 1912 at which time it was 200, and that it stayed about the same from that time until he was 70 when it began to decline. An examination during the attack of pain revealed a blood pressure of 140 systolic and 100 diastolic. There was impaired resonance and crepitant râles over both lung bases. The transverse cardiac diameter was 21 cm. The liver was four fingers' breadth below the right costal margin and tender to palpation. There was no edema. On digitalis (grs. 3 daily) all of his symptoms disappeared and he was compensated when last seen in August, 1933, after 21 years of high blood pressure. No later trace could be found of the patient in spite of earnest effort.

Patient 3. E. S., a 67-year-old white male salesman, first learned of his high blood pressure 22 years ago when, at the insistence of his wife-to-be, he had a thorough medical check-up. For the next 18 years his blood pressure varied between 180 and 220 systolic. He took no treatment nor did he follow any self-instituted régime for reduction therapy. Both he and his wife, who is also a known hypertensive, belong to hypertensive families. Both their mothers died from congestive heart failure. Her father dropped dead on the street on his 76th birthday after having had hypertension for years. His father died of a cerebral accident, also a known hypertensive. His brother and sister have high blood pressure known for many years. Her 2 sisters are known hypertensives. All have lived the usual span of life, if not longer.

This patient had a severe epistaxis in June, 1933. About 10 days previous to the acute onset of left heart failure in March, 1937, he developed a cough which persisted and precipitated the failure. Gradually he became shorter of breath than he had ever been and was very acutely ill when examined. He had a marked pallor, with cyanosis of the nail-beds. The peripheral arteries were hard, tortuous and hopping in character. There was dulness and moist râles at both lung bases. The transverse cardiac diameter was 20 cm. The cardiac rate was 140 with frequent ventricular extrasystoles. The liver was not palpable and there was no edema. The blood pressure was 190/140. A month of rest and digitalis (grs. $2\frac{1}{2}$ daily) caused all his symptoms to subside. He continued on digitalis (♏ xxxvi daily) and returned to work with dyspnea only recurring after climbing stairs. In the latter part of May, 1937, he became obstipated due to a fecal impaction which was removed rectally under nitrous oxide anesthesia. He returned to work and continued to take his digitalis daily. Twenty-two years after he learned of his high blood pressure a persistent cough precipitated cardiac failure. His blood pressure, when last seen in October, 1937, was 180/130.

Comment. The evidence submitted tends to support the statement that these hypertensive patients were simply fortunate enough to reach the arteriosclerotic age before the symptoms and signs of concomitant hypertensive heart disease appeared. The life expectancy in essential or arterial hypertension is much longer than most physicians are accustomed to believe, Fahr[4] has stated that it averages 14 or 15 years, and that heart failure in the clinical sense does not develop in hypertension until many years have passed.

Certain impressions obtained from constant contact with hypertensive patients of all types and their personal attitude toward their high blood pressure cannot and should not be discarded lightly without further consideration. The majority of these people under discussion in this analysis took their high blood pressure as a matter of fact. Few, if any, had or had had any of the symptoms so many of the hypertensives are prone to complain of in the pre-cardiac stage. Headaches, tinnitus, dizziness, "heart-burn," and constipation were not more common than among the average group of nonhypertensive patients. The psychic factor did not enter into their attitude toward their ailment. This is most important in patients with high blood pressure. Pal[11] said; "The majority of patients with hypertonicity (hypertension) have—as long as they know nothing about their illness—no, or only slight, subjective symptoms. As soon as they learn that their condition is not normal, they feel sick, complain of their troubles and seek to find complaints. They are sick nervously, and should be treated accordingly."

Ayman[1] has repeatedly emphasized this factor in the hypertensive patient. The patients in this study gave little or no heed to their high blood pressure, as evidenced by the fact they underwent no strict dietetic or medicinal reduction therapy at any time. Many of them had a distinct apathy on the subject, which at first seemed hardly possible, and this may have aided them greatly in living longer.

Of the 81 living patients 38.4% were alive 2 to 10 years after the onset of cardiac symptoms. There was a long interval between the onset of cardiac symptoms and the occurrence of congestive heart failure; but once congestive failure appeared the duration of life was short, as 77% of the 44 deceased patients lived less than 6 months after the final stage appeared (Table 3). The longer the appearance of congestive heart failure could be delayed after the onset of cardiac symptoms, the longer the patient lived. Even in such elderly patients this was accomplished with the use of digitalis and a marked decrease in activity. Over 70% of the deceased died of congestive heart failure, and this was the main factor to be delayed or controlled as well and for as long a period as possible. Even if coronary occlusion occurred, as it did in 15 (11.8%) of the 127 patients, the prognosis was good as only 3 (20%) of the 15 died as the direct result of the occlusion.

These patients had long periods free from cardiac symptoms after they learned of their high blood pressure. They also had a comparatively longer period of freedom from congestive heart failure after the appearance of cardiac symptoms. Once the failure appeared the duration of life was short, less than 6 months usually, and this final stage was not greatly extended with the use of absolute bed-rest. Digitalis was of considerable value after the onset of cardiac symptoms as it seemed to delay the appearance of congestive failure, but after the failure occurred it was of little value in relieving the signs of congestion and prolonging the life of the patient.

Summary. The course of hypertensive heart disease in 127 patients with gross arteriosclerosis, the arteriosclerotic-hypertensive group (37% known dead and 63% known living), is reported. Of these 84.3% were above 60 years, past the "hypertensive age." The known duration of the arterial hypertension was from 3 to 22 years, with an average of 12 years, but all of the patients had learned of their high blood pressure in the "hypertensive age." These patients were fortunate to live long enough to develop gross arteriosclerosis.

When congestive heart failure appeared, which was the cause of death in 71% of the deceased patients, the duration of life was short, less than 6 months in 77% of the deceased. A marked decrease in the activity of the patient and the use of digitalis (grs. 2 to 4 daily) were of considerable aid in delaying the onset of congestive heart failure and death from the time of the appearance of the cardiac symptoms.

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SPECIFIC DERMATOSES DUE TO VITAMIN A DEFICIENCY.*†

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Specific lesions of the skin caused by a deficiency of vitamin A were first recognized and described by Frazier and Hu[5a] in China, in 1931, and independently by Loewenthal[8a] in Africa and Nicholls[9a] in India, in 1933. Similar lesions, occurring under conditions of nutritional deficiency, had been described earlier but their specific relation to vitamin A was not discovered.[1,10,14,15]

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* Read in Abstract before the Meeting of the Association of American Physicians at Atlantic City, May 4, 1937.

† This study was aided by a grant from the Division of Medical Sciences of the Rockefeller Foundation.

The lesions described by Frazier and Hu[5a] consisted of dry, pigmented papules of varying size up to 5 cm. in diameter, arising at the site of the pilosebaceous follicles, principally on the extensor surfaces of the thighs and arms but extending in some cases to the shoulders, abdomen, back, buttocks and, rarely, the face and neck. The papules were conical or hemispherical and contained a central, intrafollicular plug which projected from the surface or was covered with a loosely adherent scale. When expressed the plugs left gaping cavities. The skin was generally dry, rough and wrinkled, darker than normal and often of a dull slate color. There was an absence of sweating.

The eruption described by Nicholls[9a] was similar, but in some cases the papules appeared to spread laterally producing subangular, slightly raised, flattened areas of smooth epidermis contrasting with the surrounding accentuated fissures. He named the disease phrynoderma ("toad skin") and ascribed it to vitamin A deficiency though some of his cases had dysentery and neuritis also and he thought other food deficiencies might be associated.

The papules in Loewenthal's[8a] cases presented a somewhat different appearance which he thought might be related to the degree of cleanliness or possibly to racial differences. The normal lustrous skin of the negro was dry, rough and dull grayish black. The eruption consisted of smooth-topped, black, shiny papules, about 0.5 cm. in diameter, with sharply demarcated edges and a round or polygonal shape, not coniform or obtuse as the common acne papule. The lesions were usually limited to the anterolateral surfaces of the arms and thighs with involvement of the buttocks, loins, chest and back in some cases. On the latter two surfaces they frequently merged into an acneform eruption the lesions of which differed in no way from the acne papule *except that pustulation was extremely rare*. These acneform papules were occasionally observed on the face and a similar eruption was observed by Frazier and Hu[5b] and by Nicholls. Comedones were frequent but Frazier and Hu noted that they and the acneform lesions were not found in children under 15 years of age. Pyodermic lesions were rare, especially in Loewenthal's patients, but did occur in a small number of Frazier and Hu's earlier and more severe cases.

Microscopically, the lesions were essentially identical in both Frazier and Hu's and Loewenthal's cases. The papule arose from the pilosebaceous follicle and the lumen and mouth of the follicle were dilated and plugged by a dense mass of horny, cornified epithelium arranged in more or less concentric lamellæ in which there was often a remnant of the hair. There was hyperkeratinization of the epithelium lining the follicle, hyperplasia of the adjacent epidermal cells and moderate hypertrophy of the horny layer. The cutis vera around the follicles showed a mild grade of irritative inflammatory reaction with but slight cellular infiltration. The sebaceous glands were absent or present only in remnants. The sweat glands and their ducts showed changes similar to those seen in the pilosebaceous follicles. The acne-like papules observed by Loewenthal resembled microscopically those of acne vulgaris, *except that cellular infiltration was negligible.*

Following the original reports additional studies have been made by these authors.[5b,8b,c,9b] In addition, Sweet and K'ang[13] have reported further cases from China. From India, Aykroyd and Rajagopal[3] and Aykroyd and Krishnan[2] have described a similar eruption and Radhakrishna Rao[11] has made a histopathologic study of a number of cases with findings which are essentially identical with those described by Frazier and Hu and Loewenthal. However, those Indian writers express some doubt that the eruption is due solely to a deficiency of vitamin A. Similar papular lesions in association with keratomalacia have been observed by R. E. Wright in Madras[17] and by Giblin among the Papuan natives.[6] In 1930, E. J. Wright[16] described a keratosis of the skin in what he termed cases of "A and B avitaminosis diseases" in Sierra Leone. Finally, 1 case has been reported by Goodwin[7] in London. As yet, this manifestation of vitamin A deficiency is not familiar to most American and European physicians, probably because the more severe degrees of this deficiency are uncommon in those countries and the frequent mild cases with less fully developed eruptions pass unsuspected.

During the past 2 years we have observed a number of patients with an eruption which we believe is due to vitamin A deficiency, 20 of which have been studied in some detail. Of these we have selected 6 for this report.* So far as we are aware, they are, with the exception of Goodwin's case, the first instances in white persons to be reported and the first in this country.† In nearly all the cases there was reason to suspect an insufficiency of vitamin A. In most of these this deficiency was due simply to an inadequate diet. In a few cases the deficiency was conditioned by diseases leading to a decreased intake, an improper absorption or an increased demand for the vitamin.

A part of the patients have had the dry, horny type of eruption described by Frazier and Hu. The papules, though smaller and less extensively distributed than in many of Frazier and Hu's cases were otherwise similar, grossly and histologically. In many cases the papules were no larger than those of ordinary gooseflesh. The anterolateral surfaces of the thighs and arms were most commonly

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* Two of the cases reported here were mentioned briefly in a recent article by one of us (J. Am. Med. Assn., **108**, 15, 1937).

† The 2 cases reported by Scheer and Keil[12] in this country and attributed to a deficiency of vitamin C, had lesions which were similar grossly and microscopically to the lesions of vitamin A deficiency, except for the addition of hemorrhage. As suggested by Frazier and Hu,[5b] they were probably the result of a deficiency of vitamin A, complicated by a vitamin C deficiency.

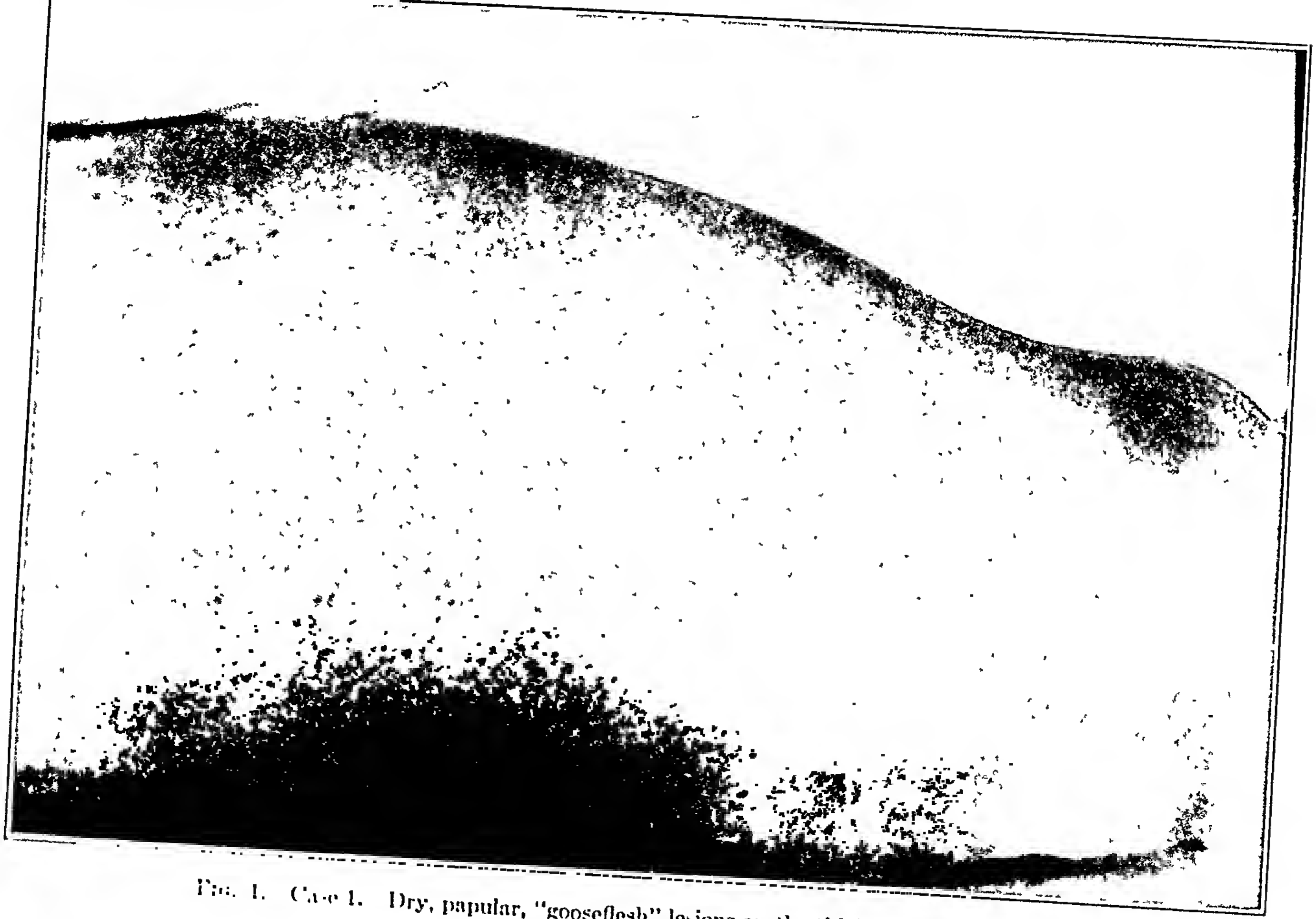

FIG. 1. Case 1. Dry, papular, "gooseflesh" lesions on the thigh; before treatment.

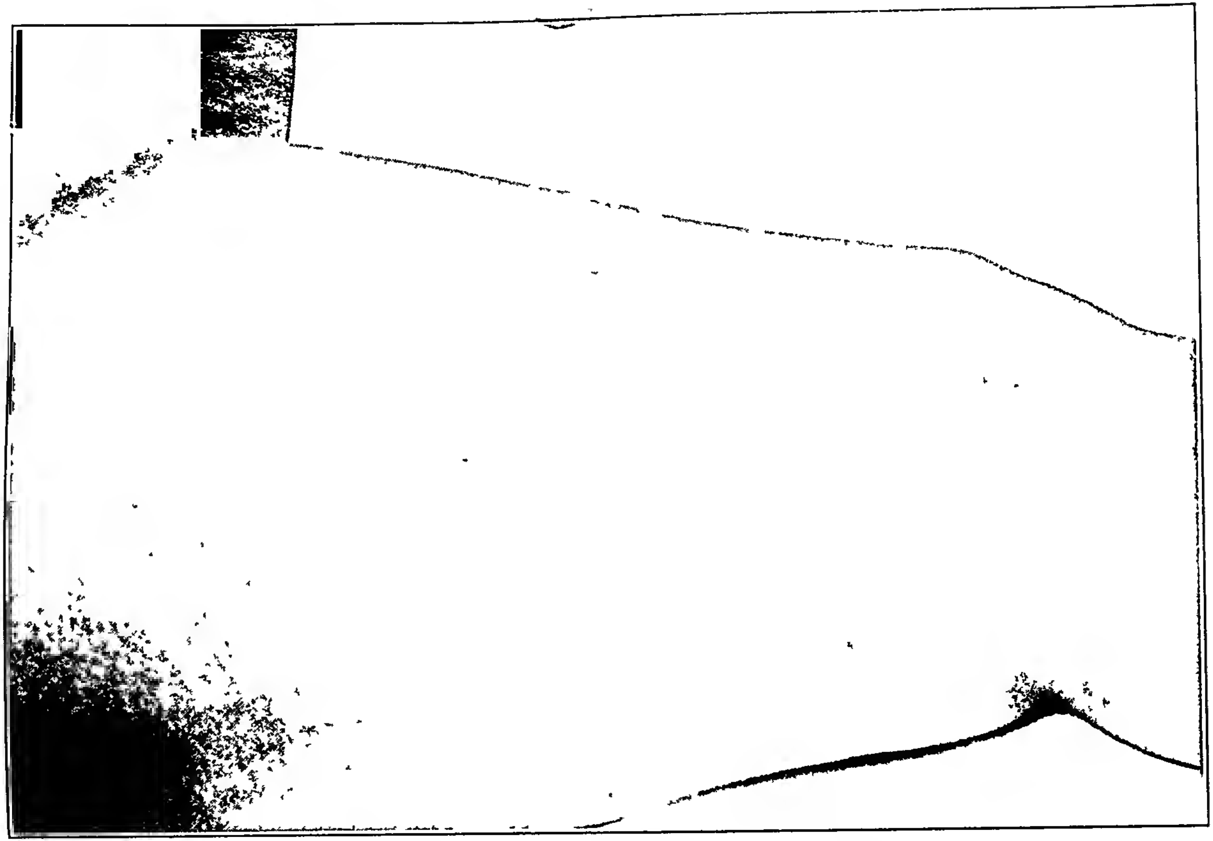

FIG. 2 —Case 1. Same region as that shown in Fig. 1; after treatment.

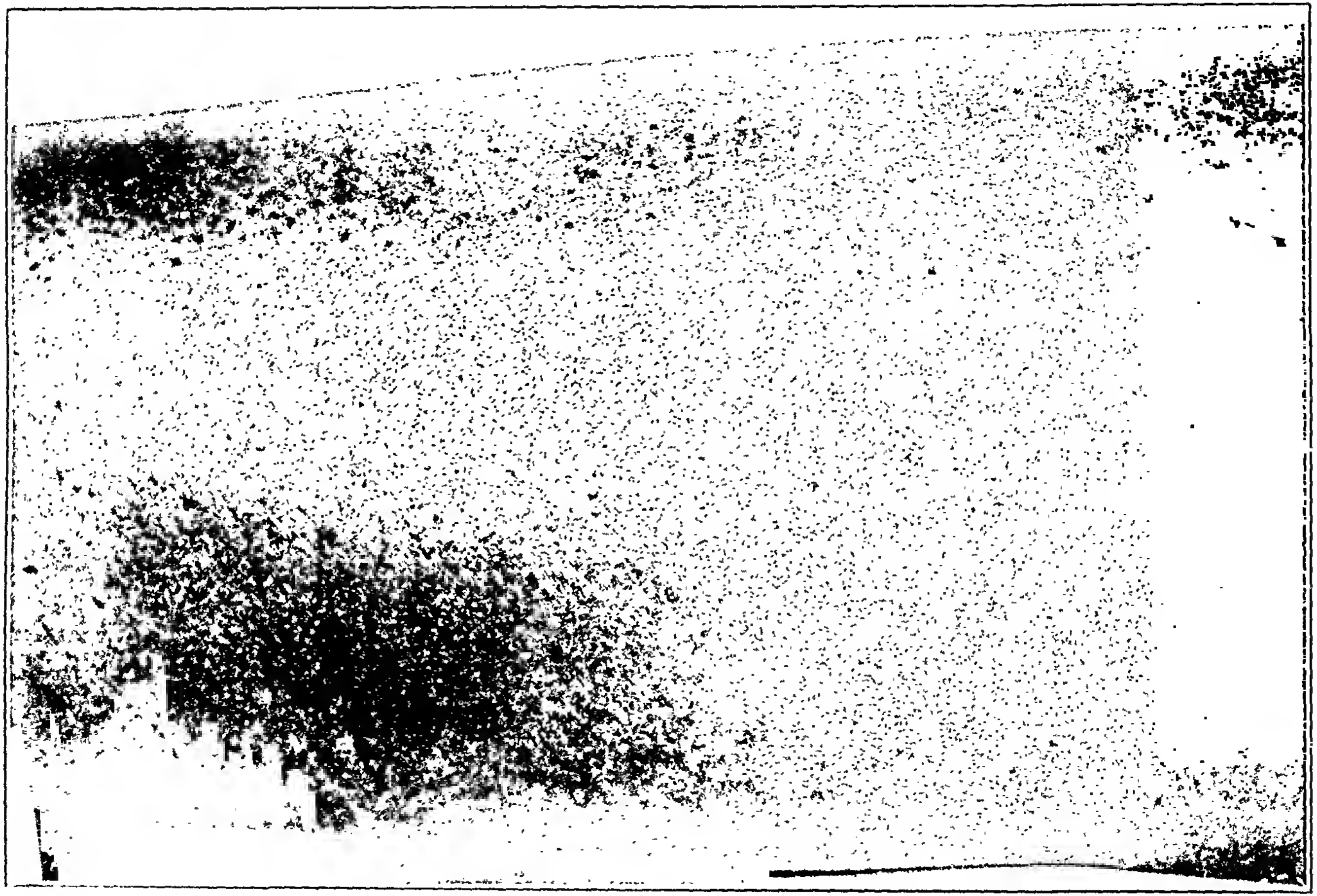

FIG. 3 —Case 2 Dry, pigmented follicular papules on the thigh; before treatment.

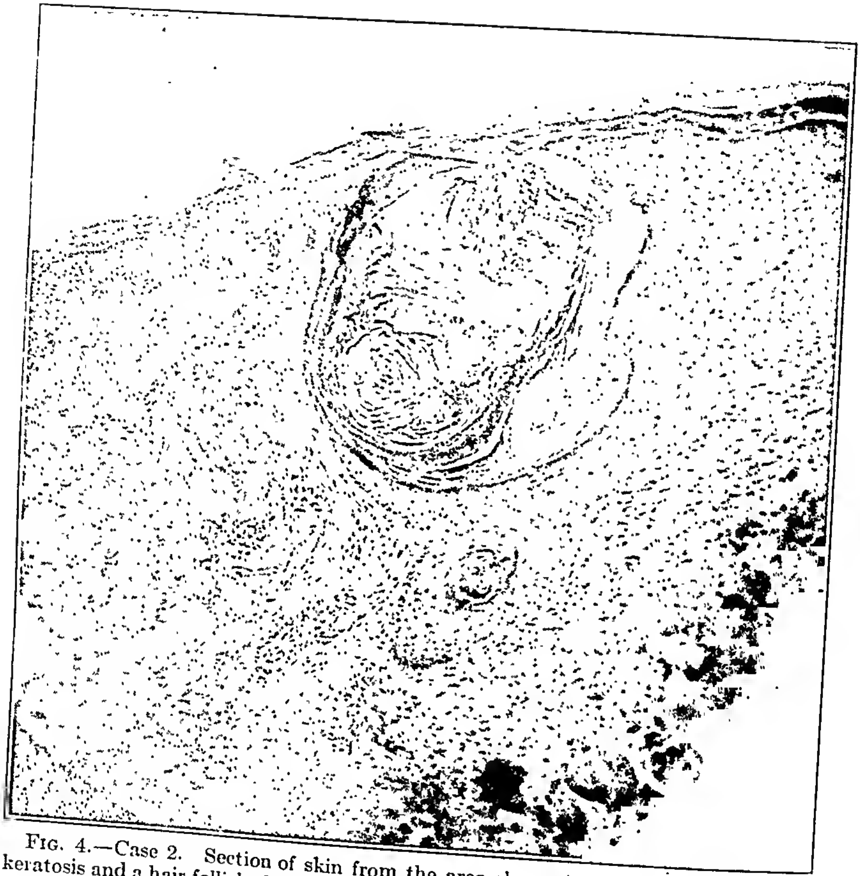

FIG. 4.—Case 2. Section of skin from the area shown in Fig. 3, showing hyperkeratosis and a hair follicle dilated with keratinized epithelium and with hyperplastic epithelium. The sebaceous gland is absent, the sweat glands are decreased in number and small. Note the absence of cellular infiltration around the follicle and lack of cellular débris within.

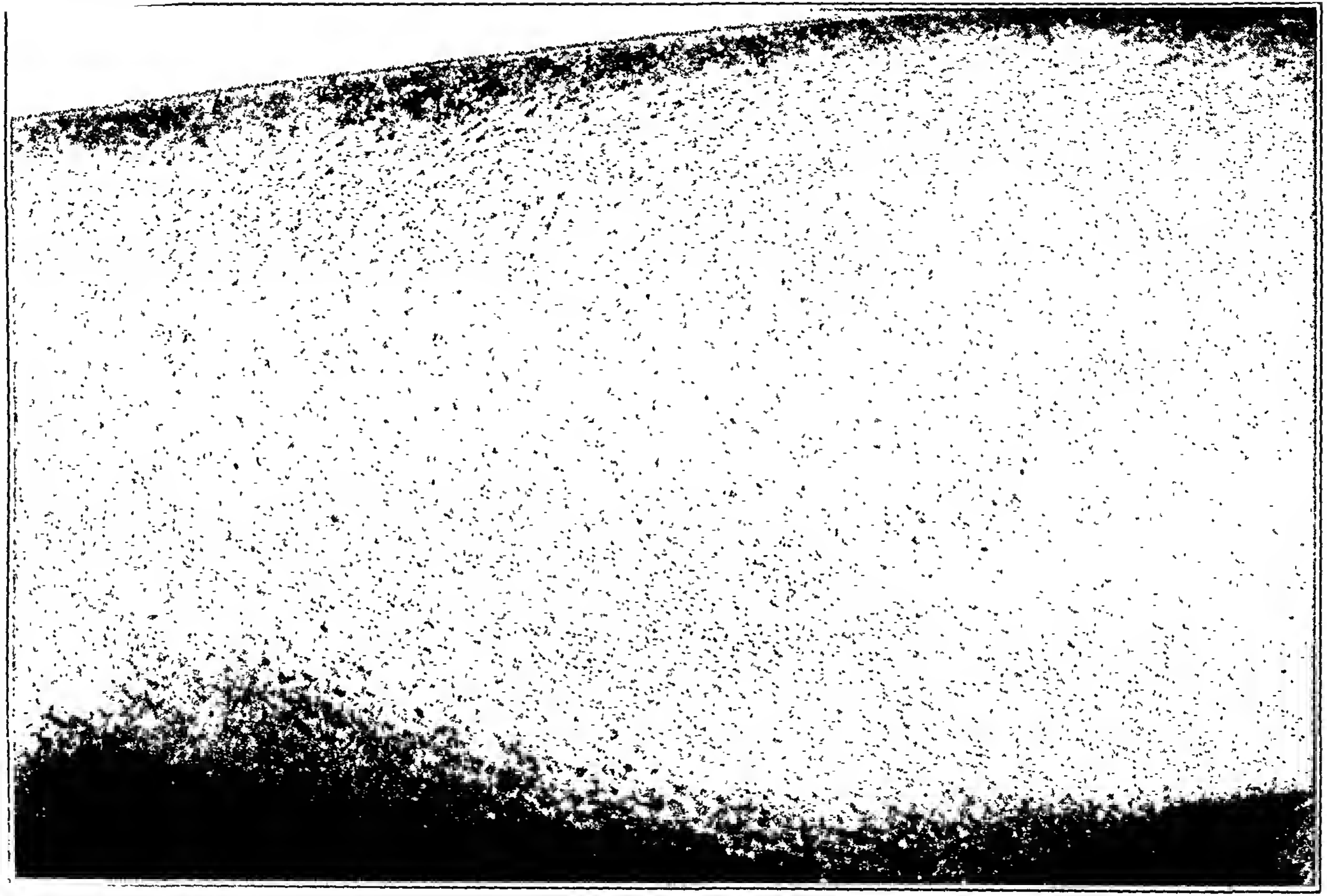

FIG. 5. - Case 2. Similar area to that of Fig. 3, showing improvement after treatment with vitamin A. There is some residual pigmentation of the site of the papules.

FIG 6.—Case 4. The arms showing the flat, rounded, red papules. The thin whitish scale can be seen on some of the lesions. Before treatment.

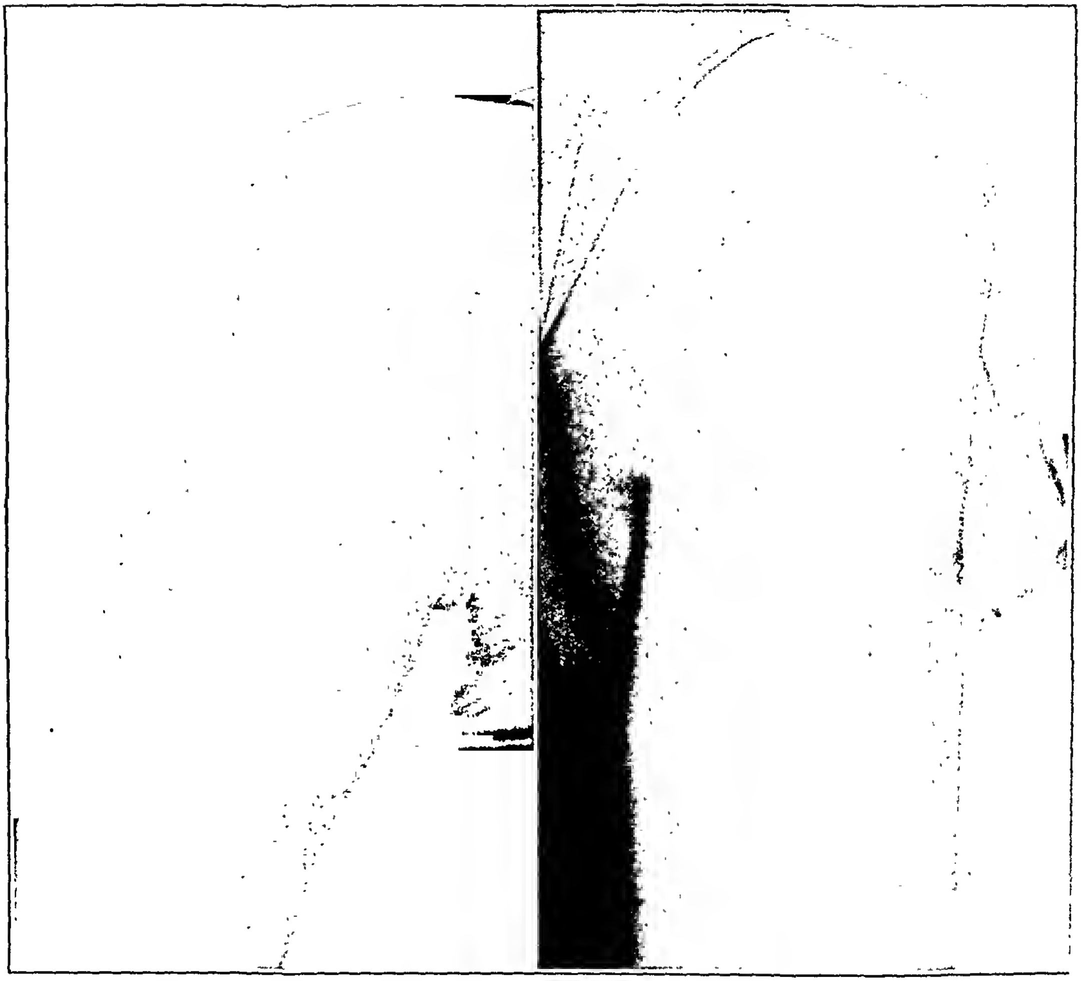

FIG. 7.—Case 4. Similar areas to those shown in Fig. 6; after treatment.

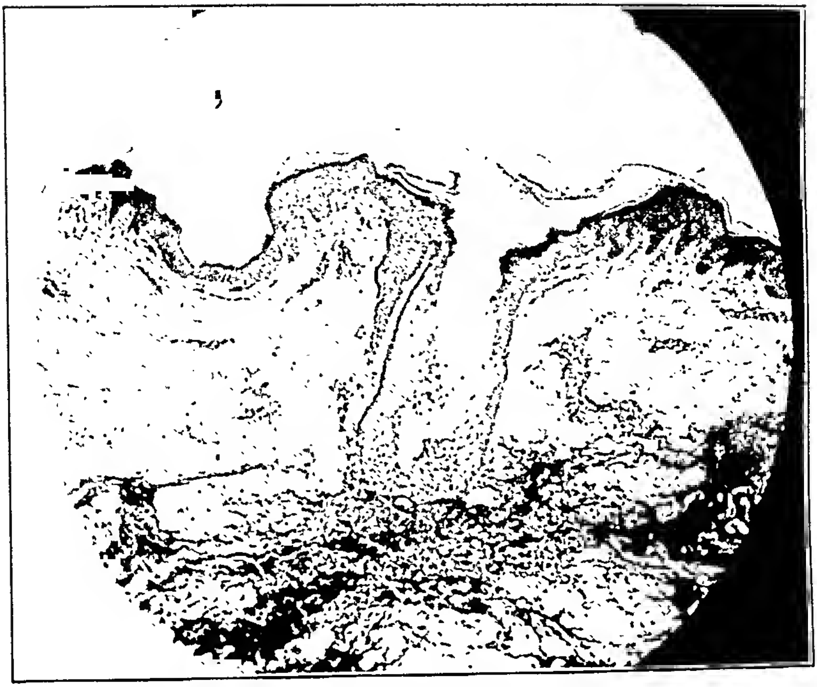

FIG. 8.—Case 5. Section of skin taken from the region of the right scapula The hair follicle is shortened and distended with keratinized epithelium which contains some cellular débris. There is a moderate infiltration of cells around the follicle.

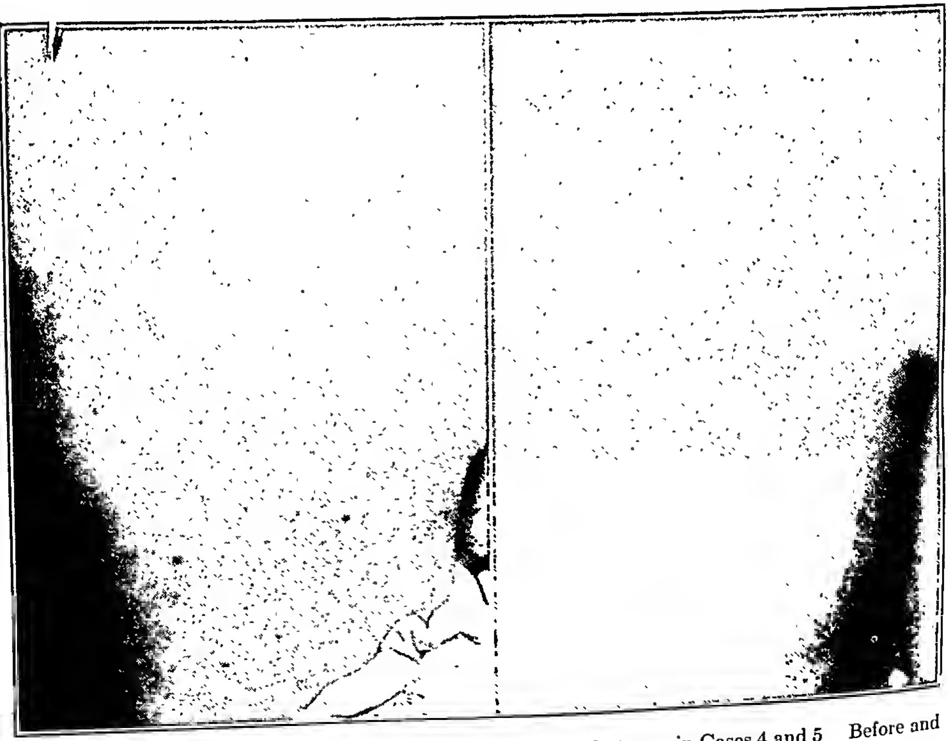

FIG. 9.—Case 6. Papular eruption on the back similar to that seen in Cases 4 and 5 Before and after treatment.

affected with the buttocks and arms next most often involved. In negroes the papules were slightly pigmented and when they disappeared under treatment left faintly pigmented scars. Pigmentation did not occur in the whites. The skin was dry and rough, especially so in the areas involved, and dull in color in the negroes. Itching was slight. Comedones were seen in some cases, presenting an incongruous appearance in the older adults, but acne-like lesions were not found in this group and infections of the skin were never observed. Bathing caused a temporary improvement in the rash making it less conspicuous but not causing it to disappear. In all the cases the eruption has disappeared or greatly improved after treatment with vitamin A. The following cases are examples of this type:

Case Reports. Case 1.—G. D., 43-year-old negress, who had attended the Out-patient Department for several years, returned, complaining of bronchitis, "pains all over," swelling of the feet, nervousness, weakness and anorexia. The food supplied by the relief agencies, although apparently reasonably well balanced, was distasteful to her and she ate little of it. On direct questioning she said she could not see to read or thread a needle and her vision was poor in the dark.

The skin was dry and rough. Over the entire lateral surface of the right thigh, part of the right buttocks and upper anterolateral aspect of the right leg there was a small papular eruption, each papule centered about a hair follicle and slightly pigmented (Fig. 1). The skin in these areas felt and looked like coarse sandpaper or gooseflesh. There were a few similar lesions on the left thigh and back. With a hand lens there appeared to be a whitish scale on the top of most of the papules. Biopsy specimens showed the characteristic changes which have been described. She was placed on cod-liver oil, 1 tablespoonful 3 times a day. Four weeks later she was much improved but it was not until about 14 weeks later that the skin had returned to normal (Fig. 2).

Case 2.—W. W., colored male, aged 29, complained of nosebleed. There was no definite history of dietary deficiency and he did not complain of a skin rash. The skin was dry and slightly scaly with a fine, horny, papular eruption over the anterolateral surfaces of the thighs and upper legs. Most of the papules were slightly pigmented (Fig. 3). Microscopic examination of a biopsy specimen showed the characteristic plugging of the pilosebaceous follicles with keratinized epithelium, absence of sebaceous glands and atrophic changes in the sweat glands (Fig. 4). He was given cod-liver oil, 1 tablespoonful 3 times a day. There was but little improvement for 12 weeks when the eruption began to regress. He was then given 16,000 international units of vitamin A daily (halibut-liver oil concentrate) and 8 weeks later the skin had returned to normal except for a residual pigmentation at the site of the lesions (Fig. 5).

Case 3.—Mrs. C. L., a white housewife, aged 48, who had formerly been treated for various gynecologic diseases returned, complaining of insomnia, "cold," cough and soreness in the chest. She could not see "half as well at night as most people." The diet had consisted mainly of beans, potatoes, turnip salad, preserved fruit and buttermilk. Over the lateral aspect of the arms and thighs the skin was dry and rough with small, dry, horny papules about the hair follicles. Histologic examination of the excised skin showed characteristic changes. She was given 12,000 units of vitamin A (halibut-liver oil concentrate) daily for 4 weeks and 25,000 units daily for 4 weeks more at the end of which time the eruption disappeared.

Other patients, all of whom are white, have presented a somewhat different eruption than that just described. It has consisted solely of dull red, flat, or slightly conical, discrete papules of varying size, usually about 0.5 cm. in diameter, similar to the acneform lesions observed in some of Loewenthal's and Frazier and Hu's cases. The papules have been distributed over the anterolateral aspect of the arms, the shoulders, upper chest and back, with few, if any, on the face, abdomen or lower extremities. The individual lesions often simulate a pustule, giving the impression that by piercing or removing the whitish top a bit of pus could be obtained. When such attempts are made, however, the cap is found to be a thin, whitish scale which, when removed, leaves a raw surface and pus is not found. In some cases there are a few scattered pustules but comedones are uncommon. The skin does not appear dry or rough and itching does not occur. Microscopically, the histologic changes are similar to those of the horny type except for a slightly greater cellular reaction. The eruption has been found in adults well beyond the age of puberty and hence beyond the usual age for acne. In no case has there been a history of preëxisting acne nor scars of a previous acne eruption. In every instance the lesions have disappeared or greatly improved following the administration of vitamin A.

Case 4.—P. S., a 20-year-old white girl, was first seen in July, 1935, complaining of tiredness. The skin was clear at this time but about 3 months later she was found to have a mild diabetes and at the same time she complained of a rash. Examination showed an eruption which was diagnosed as acne vulgaris though it was thought to be atypical. There was some difficulty in following the prescribed diabetic diet, particularly in securing 5% vegetables, and the eruption becomes worse in spite of local treatments. At this time examination showed a number of scattered, dull red, rather flattened papules over the anterolateral aspect of the arms, the shoulders and upper back, with a few on the face. Among these lesions were occasional inflammatory papules which appeared to be an ordinary folliculitis (Fig. 6). A biopsy was done but the specimen was technically unsatisfactory. She was given cod-liver oil, 3 tablespoonsful daily and in 8 weeks the eruption had entirely disappeared (Fig. 7). On discontinuing the cod-liver oil the eruption returned in about 10 weeks, but disappeared after 8 more weeks' treatment with cod-liver oil.

Case 5.—Mrs. M. K., a 25-year-old housewife, whose diet appeared to be inadequate with respect to vitamin A, complained of an eruption over the upper chest, front and back. None of the lesions was pustular. Biopsy was done and the microscopic findings are shown in Fig. 8. She was given 25,000 international units of vitamin A (halibut-liver oil concentrate) daily and in 8 weeks the eruption had entirely disappeared.

Case 6.—Mrs. E. Y., a 26-year-old white housewife, came to the clinic on May 16, 1936, complaining of "funny swimming feelings." For 3 years she had had a poor appetite and ate poorly. On examination the complexion was swarthy, the skin dry. Over the back and shoulders there was a scattered small, red, papular eruption with an occasional pustule and a number of pigmented macules. The skin of the face was clear. She was continued on the same diet and given 12 cc. of cod-liver oil daily. Ten weeks later the skin was entirely normal (Fig. 9).

Discussion. There can be little doubt of the specific relation of the lesions described by Frazier and Hu and by Loewenthal to vitamin A deficiency, though some writers have discussed the possible influence of other nutritional deficiencies. In Loewenthal's cases, particularly, the evidence indicates almost conclusively that these eruptions were due to vitamin A deficiency and vitamin A deficiency alone. As Frazier and Hu have pointed out, they are part of the widespread manifestations of this deficiency and are characteristic expressions of its effect on the epithelial tissues of the body. Nevertheless, it is possible that in some patients the eruption due to vitamin A deficiency is modified or complicated by the effect of other deficiencies, some of which also cause lesions of the skin. Multiple deficiencies are more common in practice than single deficiencies and eruptions representing combined deficiencies probably occur. The cases described by Keil and Scheer were probably of this nature. However, the essential changes due to vitamin A lack appear to be distinctive and characteristic.

In our patients with the horny or gooseflesh type of eruption the similarity of the lesions, grossly and histologically, to those described by Frazier and their response to treatment with vitamin A, identify them as a specific dermatosis due to vitamin A deficiency. In our other cases, the specific relation to vitamin A deficiency is perhaps less certain. Grossly, the individual lesions resemble in many, but not all respects, the acne papule, with the important exception as noted by Loewenthal and by Frazier and Hu, that pustulation is uncommon. Furthermore, the eruption has occurred in adults well past the acne age, without a history or scars of preëxisting acne and the affected areas are those less commonly involved by acne. Histologically, the lesions have differed from the other type only in a slightly greater cellular reaction. Finally, the eruption has disappeared following the administration of vitamin A. For these reasons, we believe the eruption is specifically related to vitamin A deficiency, the differences between it and the dry, horny type possibly due to such factors as personal cleanliness.

The relation of these changes in the skin to the other manifestations of avitaminosis A is of considerable importance. Xerophthalmia and hemeralopia were present in most of Loewenthal's cases and in many of Frazier and Hu's. Cornification of the epithelium of the conjunctivæ was observed by the latter in patients with less severe lesions of the eye. In Nicholls' cases there was night blindness. In none of our cases were there changes in the epithelium of the eye, and only occasionally was there a questionable history of mild night blindness. Studies with a visual photometer in some of our subjects demonstrated an occasional mild hemeralopia. Blackfan and Wolbach[4] and others have shown that the manifestations of vitamin A lack are evident in the epithelium of many tissues and organs and that these changes vary in respect to the order of their appearance, and their severity. Although the changes in the eye and in the vision have been thought to be the earliest reliable clinical manifestations of vitamin A lack, our observations as well as those of Frazier and Hu suggest that in some instances the skin lesions may be among the first clinical evidence of the deficiency appearing before demonstrable changes in the epithelium of the eye and before more than a mild hemeralopia detectable only by a photometer, is present. If so, these changes may constitute one of the earliest signs of vitamin A deficiency, fortunately easily recognizable.

The time required for the eruption to disappear under the influence of treatment with vitamin A is of practical importance. Improvement is seldom noted in less than 4 weeks and in many instances 12 to 14 weeks are required before the eruption has disappeared. Night blindness or difficulty in adaptation to darkness, which is also an important diagnostic sign of early vitamin A deficiency and an index of response to treatment apparently requires only the presence of an adequate supply of vitamin A and can be corrected very quickly. Resolution of the lesions in the skin, which involves a slow process of anatomic repair, takes much longer and treatment should be continued long after the visual abnormality has been corrected. The slowness of response of the eruption to treatment is also a factor which must be taken into consideration when the response to treatment is used in diagnosis.

Summary. The occurrence of dermatoses due specifically to a deficiency of vitamin A is reported together with illustrative case reports including histologic studies. Some of the cases presented the dry, horny, papular type of lesion described by Frazier and Hu, Loewenthal, and others. Other cases presented an acne-like lesion and differed in some respects from those previously described. The histologic picture and the response to treatment with vitamin A was similar in the two types of cases. The relation between these dermatoses and other expressions of vitamin A lack particularly with reference to the diagnosis of mild or early vitamin A deficiency, is discussed.

We are greatly indebted to Dr. George S. Johnson, Associate Professor of Surgery, for performing the biopsies and assisting in the histological study.

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PERIARTERITIS NODOSA.

REPORT OF CASE DIAGNOSED CLINICALLY AND CONFIRMED BY NECROPSY.

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PERIARTERITIS nodosa is a rare disease. About 20 cases have been diagnosed clinically since Kussmaul first described the disease in 1866. Many cases are missed. Though there has been some discussion as to the propriety of regarding it as a clinical entity, the typical microscopic lesions entitle it to be regarded at least as a pathologic entity. It has been associated with allergic states, with acute rheumatic fever, and the suggestion made that it is a form of hyperergy to some bacterial organism, but we are really in the dark as to its etiology. The disease is usually fatal and no age is exempt. If the heart and kidneys are not involved and if the disease is confined to less vital structures, complete cure is possible once the lesions have healed and there is no recurrence. When vital organs are involved, while the patient may survive the acute stage, he will eventually die of cardiac or renal failure due to the healed arteritic lesions. The average duration has been 4 to 6 months. Acute cases were sick for only several days.

Etiology. The cause is unknown. The clinical course with fever, leukocytosis, etc., suggests an infection. A bacillus, a filterable virus, syphilis, rheumatic fever, and allergy have been mentioned by various writers; but neither bacteria nor spirochetes have been demonstrated in a lesion. The disease has been found together with acute rheumatic fever with Aschoff bodies in the myocardium.[3] Allergy has been implicated by several histories of cough, hay fever, or asthma, and by associated eosinophilia. Cohen, *et al.*[1] have shown the similarity in the vascular lesions found in the histamine reaction, the ordinary allergic wheal, and in periarteritis nodosa. The lesions in the former two are reversible, whereas in periarteritis nodosa they are irreversible.

Pathology. The lesions are found in the smaller arteries. These are sometimes recognizable grossly as firm, smooth, yellowish to red nodules found along the course of the vessel, placed at intervals, varying in size from one to several millimeters. Surrounding the nodules may be hemorrhage, infarction, or degenerative changes in the area supplied. On cut section, the lesion may be recognized grossly at times. Purplish nodular lesions have been recognized in the mesentery at laparotomy. Most often the diagnosis can only be made microscopically. One sees an inflammatory lesion, acute or chronic in nature depending on the age of the lesion. In the acute stage, there is necrosis of the media with destruction of the muscle and elastic membrane in whole or in part. This may extend to the intima and the adventitia. At the same time there is marked infiltration of all coats of the vessel wall and the perivascular tissues with neutrophils, lymphocytes, and at times many eosinophils. There is edema and fibrin exudation. Localized weakening of the wall leads to aneurysm formation. Intimal involvement leads to thrombosis. Aneurysms may rupture and produce fatal hemorrhage. Thrombosis leads to infarction. Healing is by fibrosis and absorption of exudate. The healed vessel wall shows marked thickening and narrowing of the lumen. The reduced blood supply impairs the function of the tissue supplied and thus the signs and symptoms are produced. While typical lesions are found in the medium-sized arteries, there may also be found in skeletal muscle pericapillary infiltration of neutrophils, small round cells, and eosinophils. In our case a muscle biopsy revealed an acute focal myositis with such pericapillary infiltration (Fig. 2).

Clinical Features. The general symptoms are those usually accompanying an infection, namely, irregular fever with sterile blood cultures, prostration in the acute, and weakness, cachexia, secondary anemia, in the chronic form. Fever in the acute form is high; in the chronic, it ranges from 99 to 101° F. If cardiac involvement is present, the pulse may be disproportionately high. Leukocytosis ranges from 12,000 to 50,000. Eosinophilia is said to occur in about 12% of the cases with differential percentages ranging from 4% to 77%.[2] The blood pressure is normal if the kidneys are not extensively involved, and high if they are. The hypertension may return to normal when the process in the kidneys has subsided and the patient recovers. The hypertension, since it may be of short duration, need not produce cardiac enlargement. Added to these general phenomena are the signs and symptoms due to vascular lesions in the affected organs. Any combination of organs is possible and so the clinical picture may be exceedingly bizarre. Cardiac involvement produces symptoms of coronary sclerosis; involvement of skeletal muscles causes cramp-like pains, usually worse at night; involvement of peripheral nerves produces signs and symptoms of peripheral neuritis; involvement of appendix and gall bladder produces symptoms in the respective quadrants. Kidney involvement produces the urinary findings of nephritis. Or, there may be sudden painless hematuria when an aneurysm ruptures. Perirenal hemorrhage produces pain and mass in the lumbar region. The skin manifestations are varied. Transient erythema with subcutaneous nodules may appear anywhere. Petechiæ, purpura, ecchymoses have been described. Papulovesicular lesions over bony prominences like the knuckles and elbows may occur. These become pustular and finally hemorrhagic. They were present in our case (Fig. 1). The association of such skin lesions with evidence of heart or kidney disease, or severe asthma, or with abdominal symptoms, or peripheral neuritis, or diffuse central nervous system

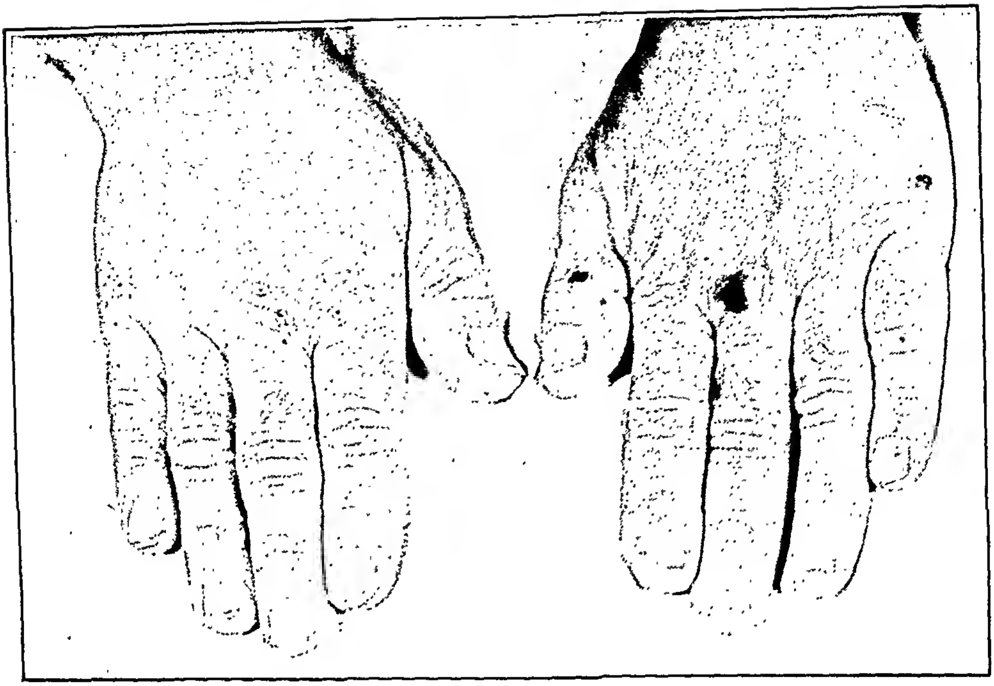

Fig. 1.—Vesiculohemorrhagic lesions of the hands; those on the left hand are fresher lesions. Similar lesions found over the olecrana and patellæ.

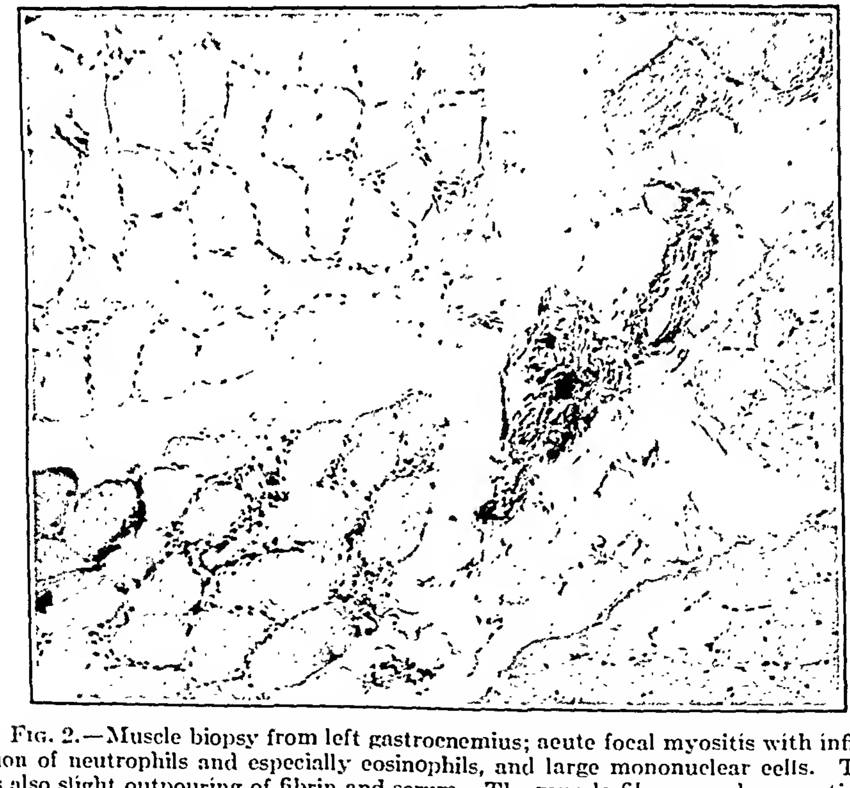

Fig. 2.—Muscle biopsy from left gastrocnemius; acute focal myositis with infiltration of neutrophils and especially eosinophils, and large mononuclear cells. There is also slight outpouring of fibrin and serum. The muscle fibers are degenerating.

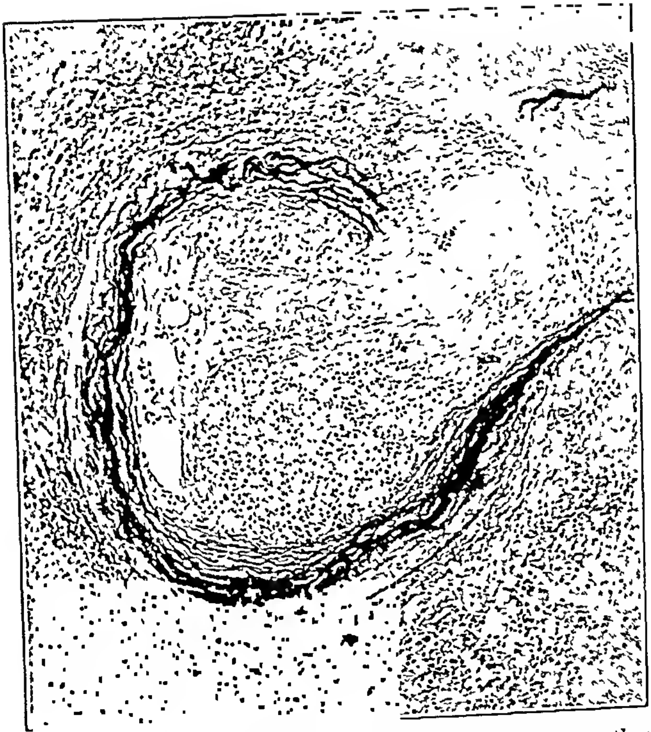

FIG. 3.—Spleen. Van Gieson elastica stain; acute panarteritis with necrosis of vessel wall and thrombosis, disruption and fragmentation of the elastic membrane

disease, should make one think of periarteritis nodosa. Edema, if generalized, may be due to cardiac or renal failure; if localized, it is probably due to involvement of the subcutaneous vessels in that area. Involvement of meningeal vessels has been reported. The spinal fluid contained numerous polymorphonuclears but no organisms.

Case Report. Patient was a white male, aged 54, born in Russia, and in the U.S.A. for 35 years. He was a tailor, married, with wife and 4 sons living and well. He had influenza in 1919. He had a mild throat-clearing cough for many years, non-productive. His present illness began in the winter of 1935 when his cough became worse. In April, 1936, he passed bright red blood in his urine. This lasted for 1 day, was painless, and never recurred. During the summer he lost 8 pounds while on vacation. In July, he had a "rash with lumps under the skin of the forehead and scalp" which lasted for 2 weeks. No physician was seen. In September, he had a severe sore throat with marked regional adenopathy. He became progressively weaker, lost his appetite, and became very constipated. About October 1st he had an attack of precordial pain radiating down the left arm but with no collapse. He was able to visit his physician who told him he had a "heart attack" and advised bed-rest. Soon pains in the forearms appeared and these lasted about 2 weeks. He remained in bed all during October, 1936.

Pains in the calves came on and these were worse at night. They were described as deep and tearing, preventing sleep. This was treated as rheumatism. The patient was first seen by the author on November 19. At this time he complained of insomnia, anorexia, weakness, nervousness, constipation, cough, dryness of the nose, and severe cramps in his legs.

Physical Examination. The scalp was normal; the pupils and fundi were normal. On the inner aspect of each cheek near the opening of the parotid duct was an ulcer, the size of a nickel, and about ¼ inch deep. The regional cervical nodes were enlarged and tender. The heart was not enlarged to percussion, the sounds were of good quality and no murmurs were heard. The rate was 110 and out of proportion to a rectal temperature of 100. The blood pressure was 138/80. The lungs were normal. Abdomen was soft, non-tender, liver and spleen not felt. The testicles were small, non-tender. There was male distribution of pubic hair, and the cremasteric reflexes were present. Over the knuckles of the fingers (except thumbs) were nodular circumscribed non-tender lesions about ½ cm. in diameter. Some were vesicular, some pustular, some hemorrhagic, similar lesions were present over the elbows and knees. The muscles of the legs were flabby, atrophic, and tender on deep pressure. The deep reflexes were present and sensation was normal. The dorsal pedis pulsations were good. Because of the buccal ulcers and the skin lesions, a blood dyscrasia was suspected. A blood count revealed: Red blood cells 3,500,000, hemoglobin 55%; no abnormal red cells; white blood cells 21,000, polymorphonuclears 88%; eosinophils 55%; neutrophils 33%; lymphocytes 12%. No abnormal white cells were found in this and subsequent counts.

The patient was then admitted to this hospital on November 23, where he remained until December 5. While there the buccal ulcers responded to treatment with mouth washes and the skin lesions disappeared without scarring. He was given a high-protein, high-carbohydrate, and high-vitamin diet. The cramps in the legs continued. He ran a low-grade fever of 99 to 101°, with persistent tachycardia of 110 to 130. There now appeared attacks of pain in the right upper quadrant and the lower abdomen. There was no nausea or vomiting. There was only slight rigidity and tenderness. The urine showed a trace of albumen: the blood Wassermann test was negative. Agglutinins for typhoid, brucellosis, para A and B were absent. The basal metabolic rate was +1. Roentgen rays of long bones were negative and those of the chest revealed slight fibrosis of the apices. Sternal puncture revealed no abnormality in the marrow. The fragility and tourniquet tests were normal. He was discharged on December 5 with no definite diagnosis. About December 7 periarteritis nodosa was thought of and a search for subcutaneous nodules revealed several on the volar aspects of the fingers opposite the distal interphalangeal joints, very slightly tender on pressure. A nodule was removed, but on histologic examination was too necrotic to warrant any diagnosis. December 10, a subconjunctival hemorrhage appeared in the right eye with much pain and epiphora. December 15 he had a sudden severe frontal headache which lasted 20 hours. A large ecchymosis appeared in the region of the left external malleolus. December 25 the buccal ulcers recurred, December 29 he was given 500 cc. of blood, and muscle biopsy was taken from the right calf. This did not reveal the classic lesion but did reveal a focal myositis with pericapillary infiltration (Fig. 2). January 21, on getting out of bed, he felt his left arm and leg to be weak, numb, and heavy. He was unable to stand. Examination revealed a left hemiparesis with left facial of the upper neuron type, with absent left abdominal reflex and positive left Babinski. He was mentally clear. He was rehospitalized. On January 25 a fresh ulcer appeared on the inner aspect of the left cheek with much swelling of the left side of the face. Blood examination revealed total white cells to be 14,000 with 70% neutrophils and a rare eosinophil. The patient became toxic and more drowsy; the temperature rose to 103°. It was now felt that he had a septicemia from the cellulitis of the left cheek. He died in coma on January 28. Final Clinical Diagnosis: Periarteritis nodosa; terminal septicemia following thrombophlebitis of the left angular vein.

Autopsy and Histologic Findings (Autopsy performed and sections examined by Dr. J. C. Ehrlich, Director of Laboratories, Lebanon Hospital).

Heart. The pericardial cavity contained 200 cc. of slightly turbid serous fluid. The epicardial surface was smooth. Shining through the epicardium could be seen several small punctate depressions indicating myocardial scarring. Sections of the myocardium showed extensive fibrosis despite the fact that the coronary arteries which were mildly sclerotic and narrowed, did not show any occlusion so far as they could be dissected. The right and left ventricles were slightly hypertrophied. The great vessels leading to and from the heart showed no abnormalities. The valves in both chambers were normal.

Lungs. The trachea and bronchi showed an intensely congested mucosa with actual necrotic patches. Both upper lobes of the lungs showed evidences of separated adhesions, and beneath these adhesions were subpleural anthracotic and partly calcified and tuberculosed scars. Within the right upper and middle lobes numerous miliary nodules were found on section. These nodules were firm and raised and could not be crushed. Some of them had the appearance of thickened small arterioles. A few similar nodules were found in the left lung. Otherwise the lungs were negative except for congestion.

Liver. The liver weighed 1350 gm., and was normal in shape. The capsule was smooth and showed several areas of discoloration. On section, the liver showed a striking picture, characterized by scattered irregular areas of red and gray necrosis and numerous very prominent small branches of the hepatic artery. The prominence was due to marked thickening of the vessel wall and in some cases a pin-point lumen could be recognized macroscopically. The bile passages appeared normal. The gall bladder was normal in size. The mucosa showed numerous shallow erosions. No nodules were seen along the cystic artery.

Spleen. The spleen weighed about 150 gm. and was very soft. On section, it had the soft grayish appearance of acute infectious splenitis. In addition, the cut surface showed numerous small grayish nodules similar to those seen in the liver.

Kidneys. The capsule stripped with ease. The surfaces and cut surfaces of both kidneys was studded with raised pearly-white nodules. Some of these definitely resembled arterioles that were thickened. Kidney pelves, ureters, bladder, pancreas, testes, prostate, seminal vesicles, and adrenals were all negative grossly.

Aorta. The aorta showed slight arteriosclerotic changes. Various branches of the inferior vena cava appeared normal.

Intestine. Along the course of the small mesenteric vessels were found tiny nodular thickenings through the small and large intestine.

Stomach and Esophagus. Negative.

Microscopic Findings: Heart. The myocardium shows extensive diffuse interstitial scarring, with infiltration by leukocytes, chiefly round cells, eosinophils, with occasional plasma cells. The small coronary arteries and arterioles in the myocardium are negative, except for moderate thickening of the arteriosclerotic type in some instances. Section of the mitral revealed normal architecture. Another section of myocardium reveals a periarteritic lesion in a branch of the coronary artery. This lesion is of the chronic type, with very little cellular reaction.

Lung. Sections reveal many nodular inflammatory lesions having the appearance of circumscribed areas of bronchopneumonia, with early necrosis and suppuration of the inflammatory exudate. Near one of these areas a small branch of the pulmonary artery shows a chronic arteritis. The pleura appears normal.

Liver. Numerous sections taken from various areas reveal multiple arteritic lesions, most of which are acute. These lesions are characterized by an acute panarteritis and thrombosis, sometimes with recanalization, destruction of arterial walls in varying degrees, and inflammatory exudate containing many eosinophils, as well as neutrophils, round, and plasma cells. Periarterial inflammatory exudate is likewise present. These lesions involve mostly medium-sized arteries. The parenchyma shows cloudy swelling. Elastica stains show striking disruptions in the internal and external elastic membranes, as well as large amounts of fibrinoid material in the involved vessels. The veins appear uninvolved.

Spleen. The capsule is moderately thickened with some cellular infiltrate. The pulp shows extensive inflammatory reaction, containing great numbers of neutrophils, round cells, plasma cells, and many eosinophils. Conspicuous vascular lesions consisting of acute arteritis with necrosis of muscle wall, thrombosis, and other changes described above are found in different sections.

Kidney. Sections reveal multiple miliary abscesses throughout the cortex. Several typical panarteritic lesions are also observed. There are areas of cortical parenchyma that appear normal. One of the arcuate arteries shows striking involvement. Where renal parenchyma is relatively uninvolved by vascular lesions or by infection, the glomerular and tubular elements appear relatively normal, except for severe parenchymatous degenerative changes.

Intestine. One section of intestine shows lesions of the acute and chronic variety. The mucosa of the bowel appears normal. The arteritic lesions show periarterial inflammatory changes, but the neighboring bowel wall shows no change.

Trachea. A section through one of the main bronchi shows a large arteritic lesion which is associated with rupture of the external elastic membrane and a large periarterial thrombosis.

Gall Bladder, Appendix, Testis. Sections reveal several arteritic lesions in the medium-sized branches of the cystic artery. A section of appendix shows an acute panarteritis with thrombosis of a small appendicular artery. The mucosa and wall of the appendix otherwise appear normal. Section of testis reveals fairly normal seminiferous activity along with one medium-sized artery which is the seat of an arteritis similar to that seen in other organs.

Summary. This is a case of generalized periarteritis nodosa diagnosed clinically. The disease was complicated by terminal sepsis with miliary abscesses of the lungs and kidneys. Skin nodule biopsy was inconclusive because of the extensive amount of necrosis present. A biopsy of calf muscle was also inconclusive and showed only a slight degree of focal myositis. An unusual clinical manifestation was the appearance of buccal ulcerations which may have occurred on a vascular basis. The arteritic lesions were mainly of the acute variety, a few being of the chronic variety.

The author is indebted to Drs. A. M. Pappenheimer and Russell Holman of the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City, for study of sections of muscle biopsy; to Drs. Wm. Aronson and Jacob Taub of the Department of Pathology, Morrisania City Hospital, Bronx, New York City, for study of the skin nodule biopsy; and to Drs. J. C. Ehrlich and Sam. Forer of the Department of Pathology, Lebanon Hospital, Bronx, New York City, for performing the autopsy and study of sections from the organs.

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THE RELATIONSHIP OF SYDENHAM'S CHOREA TO OTHER RHEUMATIC MANIFESTATIONS.*

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Too many articles have been written about chorea to attempt to review the literature in this paper. We will refer only to certain papers which have appeared in the last few years which present opinions and findings somewhat at variance with the results of analyses made of patients with chorea who have been observed at Bellevue Hospital.

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* This work was made possible in part by grants from the Josiah Macy, Jr., Foundation and The Millbank Fund.

For many years, although chorea minor was recognized as an entity, it was regarded as a functional nervous disorder. Finally, its clinical association with the various manifestations of rheumatic infection was noted, and for some time the probability that there is a common etiologic factor, as yet unknown, was hardly questioned. Obviously, in the absence of knowledge as to the specific etiology a definite answer cannot be given; but until then analyses of the course of the disease and its clinical manifestations may lead to tentative conclusions.

It has been interesting to review our own conception of chorea. We have studied it intensively for 10 years. At the beginning, one of the objects which we hoped to attain was some way of differentiating between the rheumatic and the non-rheumatic attacks. After following several hundred children ourselves and reviewing the records of others whose observation period began before the present study, we have come to the opinions first, that most children with chorea are rheumatic children; and, second, that if this is not true there is no clinical means at present by which it is possible to differentiate a rheumatic from a non-rheumatic attack.

The diagnosis of Sydenham's chorea is made wholly on the basis of a certain type of peculiar extraneous muscular movement. The condition should be considered a syndrome rather than a disease entity, just as we speak of acute polyarthritis as a rheumatic manifestation and not a disease in itself. Non-infectious conditions may produce the same type of movements, for instance, intracranial hemorrhage. Other infections, such as epidemic encephalitis, if the proper area of the brain is involved, may lead to choreiform movements. In such instances, which are rare compared to the frequency of Sydenham's chorea in certain communities, the history decides the etiology of the movements. All other attacks we think should be assumed to be rheumatic in origin. The reasons for this opinion will be shown.

Source of Material. The sources of our material are patients seen in the Children's Cardiac Clinic, and on the wards of the Children's Medical Service of Bellevue Hospital. For 5 years a special chorea clinic was in existence as a subdivision of the cardiac clinic, and with a special social worker to keep track of the children. The cases are still being followed, but in the regular cardiac clinic. This study is only a part of an analysis being made of 1052 rheumatic children. A total of 467 detailed records of children who had chorea and who were subsequently under observation in the clinic have been analyzed from a number of different angles. Attacks of so-called *chorea insaniens* occur entirely among an older age group than is cared for on a Children's Service Such patients are taken to the Psychiatric Division at Bellevue Hospital. Although we are given the opportunity of seeing these adults, none of them is included in this study. The clinical picture is different, with the high fever and irrationality, from that which we see in children. We have had a few 12- to 14-year-olds who were psychotic during the acute phase of the attack, but they did not fit into the chorea insaniens classification.

Precipitating Factors in Attacks of Chorea. Before presenting the data on which we base our opinion as to the relationship between chorea and other rheumatic manifestations, we will give what information we have regarding the tradition, recently revived by Gerstley[3] and Coburn,[1] of emotional disturbance as a precipitating factor in an attack of chorea. Coburn[1] says "One-half of all cases of chorea in New York may occur in individuals who are not susceptible to rheumatic fever. . . . . Their attacks were not preceded by respiratory infections, but seemed to be associated with psychic trauma."

To find the experience of our patients, 411 records of children admitted to the hospital for chorea were reviewed for any history of possible precipitating causes of the attack occurring within 2 months of the onset (Table 1). At the time the history had been taken, this point was specifically inquired into. The cases were divided into two groups, 217 seen in the first attack and 194 seen in subsequent attacks. Emotional disturbances include fright, accident, worry about school work, and so forth. The rheumatic manifestations have been divided into frank polyarthritis, in most cases occurring about 2 weeks before the onset of the chorea, subacute rheumatic manifestations such as a period of joint and muscle pains, low-grade fever, nosebleeds, and carditis. This latter small group of patients developed chorea while in the hospital for the carditis. The non-specific infections include colds, sore throats, otitis media, scarlet fever, and other acute contagious diseases.

TABLE 1.—EPISODES PRECEDING WITHIN 2 MONTHS THE ONSET OF 411 ATTACKS OF CHOREA.

Preceding episodes	First attacks, 217.				Subsequent attacks, 194.			
	No.	%	No.	%	No.	%	No.	%
Emotional upsets			21	9.6			18	9.2
Rheumatic episodes			30	13.8			18	9.2
Carditis	3	1.4	..	..	1	0.5		
Subacute rheumatism	12	5.5	..	..	6	3.1		
Polyarthritis	15	6.9	..	..	11	5.6		
Non-specific infections			17	7.8			9	4.8
No preceding episodes			149	68.6			149	76.8

As will be seen, among the 217 patients admitted in their first attack, 21 (9.6%) had had a recent emotional upset; 30 (13.8%) had had a recent rheumatic episode and 17 (7.8%) had had recent non-specific infections; 149 (68.6%) had had no recent previous illness or emotional upset. Among those admitted in subsequent attacks the percentage of emotional factors is almost exactly the same, while the rheumatic and non-specific infectious factors are somewhat lower. While the percentages of the total groups are too small to conclude that either psychic trauma or rheumatic manifestations are closely associated with the onset of chorea, they do seem to show that psychic trauma is of no greater importance in precipitating attacks than is rheumatic activity, and of only slightly greater importance than non-specific infections. Kennedy[5] reminds us of the mental and nervous diseases once thought to be functional and now known to be on an organic basis, such as dementia paralytica and paralysis agitans. The fact that the etiology of a clinical syndrome is obscure is to us not justification to ascribe its origin to such a nebulous state as "psychic trauma" (Gertsley *et al.*) or to refuse to consider it as a manifestation of a diseased state. To quote Kennedy, "Only in Wonderland can we find the grin without the cat!"

Mentality of Children With Chorea. The mentality of children with chorea has received some attention, and Gerstley[3] found that 38 of the 45 children in his study had above the average intelligence. Our patients, on the basis of psychometric examinations, had the same intelligence as the general run of children seen at Bellevue Hospital, that is, they were with few exceptions normal or dull normal. Of 100 tested, the Intelligence Quotient of 83 was between 80 and 110, with the peak at 90 to 94; only 1 had the rating of over 125, and a number were far below normal. We have not found that children with chorea have any particular personality or body type. Most of our Bellevue patients, rheumatic and non-rheumatic, come from homes where economic security is absent, and where family discord is the rule, but this does not mean that these factors are necessarily a cause of chorea.

Is Chorea an Infection? Gerstley says "Chorea should not be taken as an indication of rheumatic infection without other rheumatic manifestations." Coburn says "Chorea *per se* does not suffice for the recognition of the rheumatic subject nor for the diagnosis of rheumatic activity."

If one believes that the accepted clinical evidences of infection are sure guides in the evaluation of symptoms, these statements are logical. However, adherence to this point of view would lead to improper care of patients who have an infection so subacute as to fail to produce the bodily responses which appear in the acute phase. To us, the fact that patients with chorea, in the absence of other clinical manifestations of rheumatic activity, do not present the usual evidences of infection such as fever, leukocytosis and increased erythrocyte sedimentation rate does not seem proof or even good evidence that the condition is non-infectious. One of our patients, reported in a previous article,[8c] who died accidentally during an attack of chorea, had none of the clinical evidences of infection or of heart disease, but at autopsy had acute endocarditis of the mitral valve. The erythrocyte sedimentation rate, in our experience is not an infallible index of activity. We have had patients with indubitable active carditis, without congestive failure, who have had normal rates throughout the course of the acute illness. We feel that the erythrocyte sedimentation rate is an aid, but no more than an aid, in coming to conclusions as to rheumatic activity, and that a normal rate is not proof of the absence of active infection. We do not agree with Coburn[1] that a normal rate should be adduced as "strong evidence against the rheumatic origin of chorea." We would like to call attention to the fact that disease processes may be present for some time, as in tuberculosis or cancer before becoming clinically manifest.

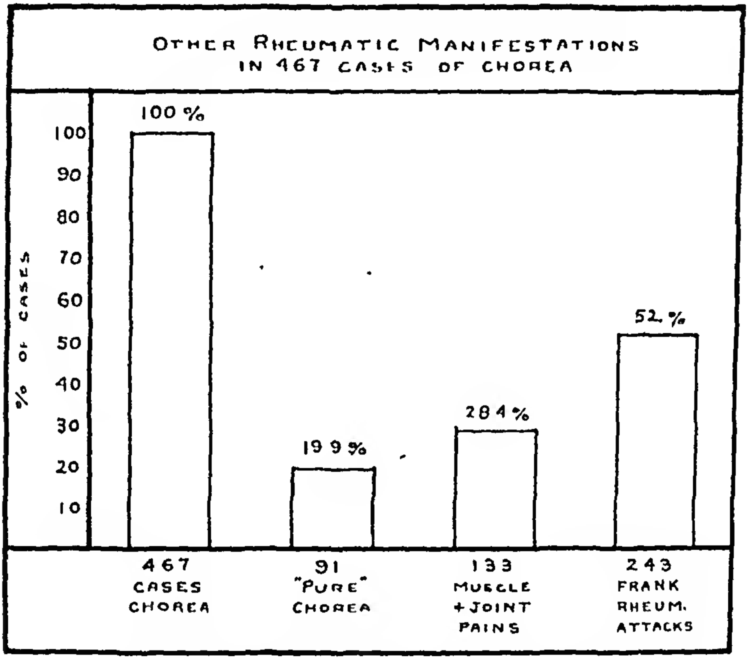

Fig. 1.—Other rheumatic manifestation in 467 cases of chorea.

The proof of an absolute relationship between Sydenham's chorea and rheumatic polyarthritis or carditis must await, as often emphasized, the finding of the cause of rheumatic fever. Until then the only way to study the question intelligently is by analyzing the course of the disease. We have approached the problem in much the same way as have other workers.

Development of Rheumatic Heart Disease in Patients With Chorea. In a group of 1052 rheumatic patients whose records are being studied, chorea was present at some time in 467 and absent in 585. Those with chorea were subdivided into those with and without other rheumatic manifestations. By "other rheumatic manifestations" we mean polyarthritis, carditis and nodules, and do not include muscle and joint pains. Although in retrospect it is frequently possible to conclude that indefinite pains were probably rheumatic in origin, it is not possible to be sure at the time the pains occur. It is for this reason that we have not considered them among the frank manifestations of rheumatic fever, but have grouped them separately.

Figure 1 shows the incidence of other rheumatic manifestations in the 467 children who had chorea. Frank rheumatic attacks occurred in 52%, muscle and joint pains in 28.4%, while 91 (19.9%) had chorea only.

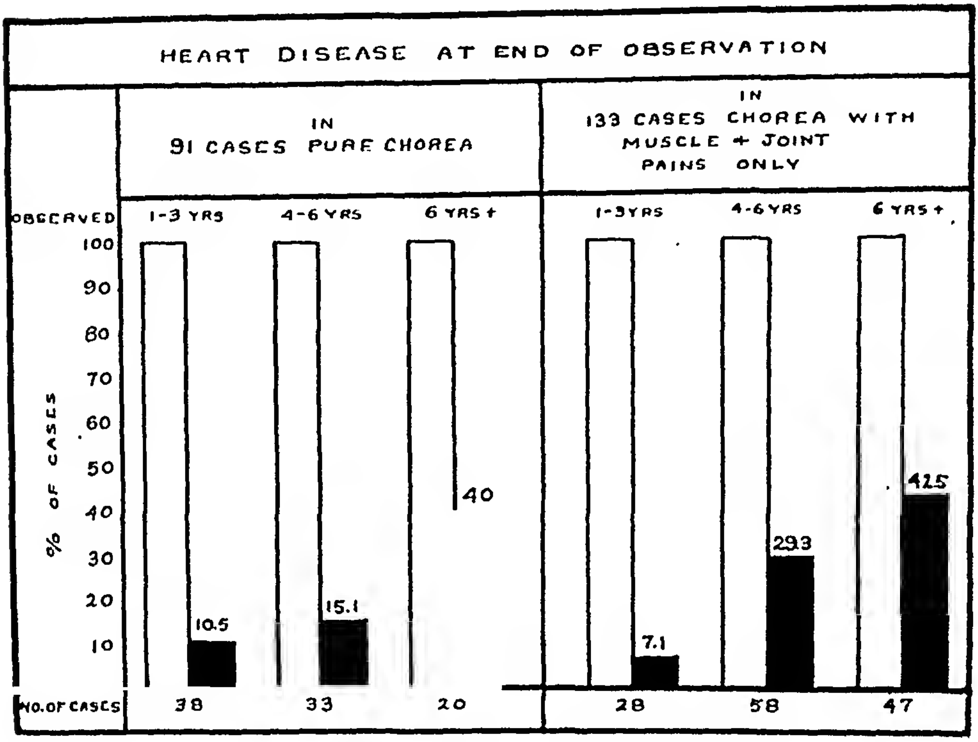

FIG. 2.—Heart disease at end of observation in 91 cases of pure chorea, 133 with chorea and muscle and joint pains.

These groups were analyzed for the incidence of organic heart disease at the end of observation. Among the 467 patients who had chorea there were 91 (19.9% of the total group) who never at any time had any other frank manifestations of rheumatic infection or muscle and joint pains. Among the 91 were 17 patients (18.6%) who had organic heart disease at the end of a mean duration of 4.8 years from the onset of the chorea. In addition, there were 133 patients who had muscle and joint pains as well as chorea, who were therefore not considered "pure" chorea. Forty of the 133 patients (30.1%) had organic heart disease at the end of observation. If these two groups are combined there were 224 (48%) of the total 567 patients who had chorea, but no other "frank" rheumatic manifestation. The incidence of heart disease in the 224 was 25.4% at the end of observation. We did not include in these groups 20 patients who had valvular disease at the time of their first attack of chorea (10 who were otherwise pure chorea and 10 who had muscle and joint pains in addition to chorea). If these patients are included there was an incidence of organic heart disease at the end of observation of 26.7% in the "pure" chorea group, and 33.5% in those with muscle and joint pains. Figure 2 shows graphically the distribution of heart disease in these two groups (*i. e.*, chorea only, and chorea with muscle and joint pains) by years' observation, and indicates that the longer the observation period the greater the incidence of heart disease.

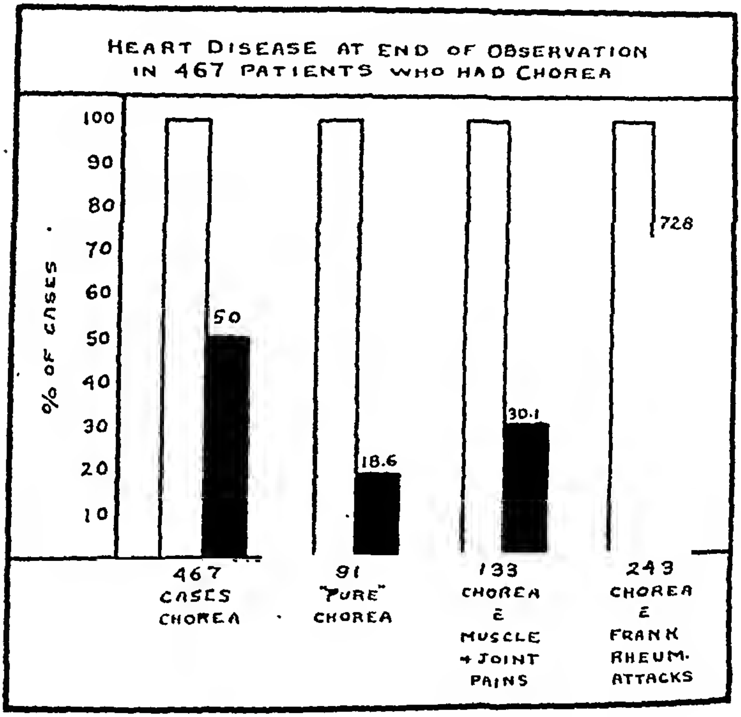

FIG. 3.—Heart disease at end of observation in 467 with chorea.

The other patients who had chorea (243) had polyarthritis, carditis or nodules either before, during or after the attacks of chorea. Of this group, 177 (72.8%) had heart disease at the end of observation. These figures are shown graphically in Figure 3. This figure may be compared with the incidence of 71.9% heart disease in the 585 rheumatic patients who never had chorea. If those with muscle and joint pains only are separated from this group there was an incidence of heart disease of 43.5% in the 108 with muscle and joint pains and of 78.4% in those with frank rheumatic manifestation (Fig. 4).

In connection with the figure for the development of heart disease in the patients with "pure" chorea (18.6% of 91 patients) we would like to emphasize the fact that we adhered closely to the criteria for the diagnosis of heart disease laid down by the American Heart Association,[2] although we feel that in some instances the presence of a mitral systolic murmur without demonstrable enlargement means heart disease. Among these 91 patients were some who received fever therapy during the first attack of chorea. We have shown[8b] that fever therapy appears to exert some modifying effect on the development of heart disease. We feel, therefore, that our findings in regard to the development of rheumatic type heart disease in patients with "pure" chorea is under rather than over estimated.

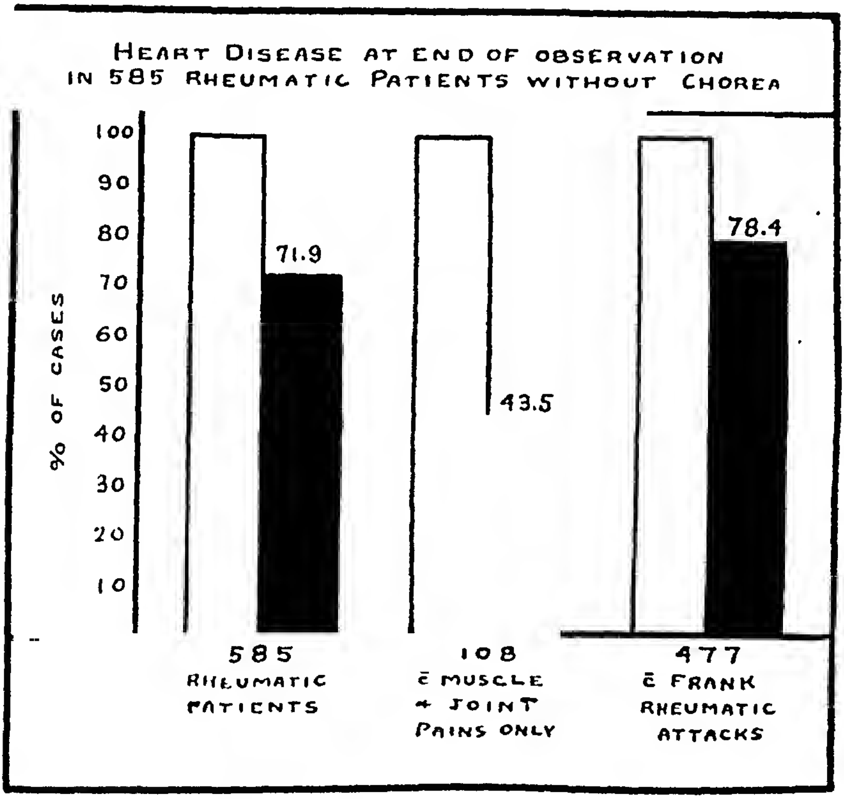

FIG. 4.—Heart disease at end of observation in 585 without chorea.

Relation of Chorea to Other Rheumatic Manifestations. We do not question the fact that chorea is not often associated with the severer forms of rheumatic infection. For instance, of 66 children admitted to Bellevue Hospital in their first attacks of rheumatic polyarthritis, 40.9% had clinical evidence of an acute carditis. To compare with these figures, 66 records of first attacks of chorea were taken at random from the files. Only 4.5% of these had active carditis. On discharge, 27.3% of the children admitted with polyarthritis had definite organic heart disease, while 13.7% of the chorea patients had this diagnosis on discharge. These figures refer only to single first attacks.

We have analyzed the course of the disease in 124 patients who had chorea as the first rheumatic manifestation and who did not receive fever treatment; 23 were under observation 1 to 3 years; 37 for 4 to 6 years; and 64 for 7 years and longer.

TABLE 2.—THE PERCENTAGE OF SUBSEQUENT ATTACKS OF CHOREA, POLYARTHRITIS, OR OF HEART DISEASE AFTER THE FIRST ATTACK OF CHOREA.*

	1 to 3 years.	4 to 6 years.	7 to 22 years.
Number of cases	23	37	64
Recurrent chorea	37.5%	51.0%	76.5%
Polyarthritis	32.0%	33.0%	48.5%
Heart disease	26.0%	35.0%	53.1%
Dead of heart disease	13.0%	10.8%	7.8%

* The data are obtained from records of patients during the period of our observation. Deaths which occurred subsequently are not included. For instance, 5 other patients observed more than 6 years died, but not under our observation. If these were included, the percentage of deaths in this group would be 15.6%.

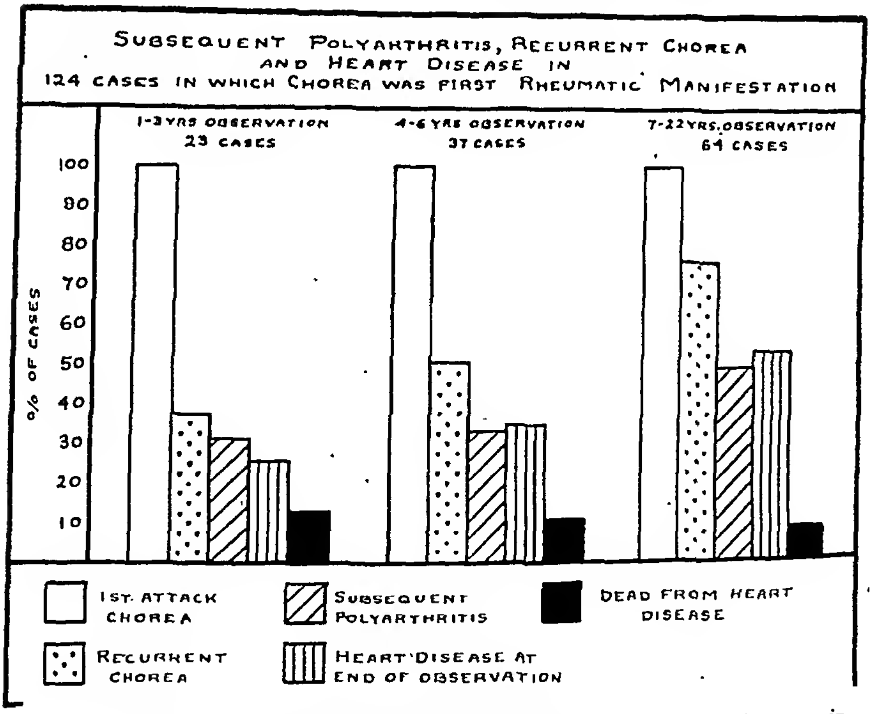

FIG. 5.—Subsequent polyarthritis, recurrent chorea and heart disease in 124 cases in which chorea was first rheumatic manifestation.

This shows that polyarthritis occurred in the subsequent course of about 50% of those who started their rheumatic career with chorea; that heart disease was present in 26% of those in the 1 to 3 year period and in 35% in the 4 to 6 year period, and 53% in those observed 7 years or longer. Figure 5 shows this graphically.

Our analysis has produced figures very similar to those of other detailed studies of chorea, with one notable exception. Jones and Bland[4] found that heart disease developed over an average observation period of 8 years in 4 of 134 patients (3%) who had chorea as their only rheumatic manifestation. They do not state, however, the exact observation periods of the patients with "pure" chorea. They use the phrase "an average observation of 8 years" for their whole group. Schwarz and Leader think, and we agree (Fig. 2), that the longer patients with "pure" chorea are observed the greater is the probability of finding that heart disease has developed. Few studies have appeared dealing with the development of heart disease in such a series of "pure" chorea. Our figure, which we feel is conservative is 18.6%; Schwarz and Leader[7] had a higher figure (52%). In our study and in Jones and Bland's, the criteria for the diagnosis of heart disease laid down by the American Heart Association were followed.[2] The difference between 3% and 18.6% obtained from similarly made analyses from presumably similar material is too great to be reconcilable. We can hardly feel that the clinical observation either on our patients or on Jones' patients were inaccurate. Since our other findings are so similar to those of the Boston investigators the material itself seems to be comparable. It would hardly be reasonable to suggest and certainly hard to prove, that chorea is less severe in Boston than in New York. It is obviously important that similar analyses should be made by other students of the disease.

Prognostic Significance of Sydenham's Chorea. One of several attitudes may be taken in evaluating the seriousness of chorea. Most important is the effect on the patient's future life and health. Our figures, and those of others, indicate the high probability of further attacks. Our figures, and those of others, indicate the probability of attacks of polyarthritis and carditis occurring in patients who have had chorea. Our figures indicate an 18.6% probability that rheumatic heart disease will develop in patients who have had chorea as the only manifestation of rheumatic infection. This is the most serious factor to be considered.

We interpret the fact that chorea is not as intimately associated with attacks of acute carditis either at the time or subsequently to mean that the rheumatic infection is not as severe in such individuals as in those who respond in terms of an attack of polyarthritis or carditis. We think it should be spoken of as one of the rheumatic manifestations, rather than a condition which "seems to play but a small rôle in the development of heart disease of the rheumatic type" (Jones and Bland) or to use the phrase which Roth[6] did in suggesting that "valvular heart disease in cases of chorea is due not to chorea but to intercurrent episodes of polyarthritis and carditis." In other words, chorea is, to us, an evidence that the patient has been attacked by the same infection which produces rheumatic heart disease, not that chorea causes heart disease. This is more a matter of phrasing rather than a difference in fundamental conception, but accurate expression of an idea leads to clearer thinking than loose expression.

We do not take exception to Jones and Bland's opinion that an attack of chorea is not usually a serious condition in terms of survival of the attack; but our experience has been different from theirs in regard to chorea occurring during the terminal illness. They state that of 50 deaths in their series of rheumatic patients none had chorea in the last illness. We have had a number. The most recent and striking was a 7-year-old boy admitted desperately ill with pericarditis. Soon after entrance in the hospital he developed choreiform movements which progressed rapidly to a severe state. He died within 2 weeks of onset of the illness. He had had one previous attack of chorea in Bellevue Hospital at the age of 2 years and 10 months, and had been perfectly well and free from any clinical evidence either of chorea or heart disease in the *interim*. Such cases are not numerous, but do occur.

We think we are not justified in drawing definite conclusions from the evidence presented here, but that we have some basis for our opinions which are summarized below.

Summary. 1. Sydenham's chorea is not usually *per se* a serious condition.

2. Rheumatic heart disease develops in approximately 20% of patients who have had chorea as the only clinical manifestation of rheumatic infection.

3. The child who begins his rheumatic career with chorea runs a 50% chance of developing heart disease.

4. The child who begins with chorea runs a 50% chance of developing other rheumatic manifestations later, or if muscle and joint pains are included a 75% chance.

5. Emotional factors are no more important, and probably less so, in initiating an attack of chorea than preceding acute infection, including rheumatic polyarthritis.

6. Chorea should continue to be regarded not only as a manifestation, but as a major manifestation of rheumatic infection.

We wish to express our appreciation to Miss Claire Lingg, Miss Harriet Steinhilber and Miss Ethel Brown, of The Research Service of The New York Heart Association, for their invaluable help in collecting and analyzing the data presented in this paper.

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BLOOD CULTURES AFTER TONSILLECTOMY.

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Seifert,[13] in 1925, attempted to determine whether a significant bacteremia occurred after operation in an infected field. By taking a blood culture within 10 minutes after incision and drainage of various abscesses, he obtained from the blood stream in 45% of his 204 cases the same variety of organism that was present in the abscesses. Moreover, in 43 cases of acute appendicitis without peritonitis, he recovered the organism from the blood after appendectomy in 9 instances (21%). Similar studies of patients undergoing tonsillectomy have been made by Rubin, Epstein and Werner,[11] Schwarz and Frisch,[12] Bartlett and Pratt,[2] Wirth[15] and Fischer and Gottdenker.[5] Their results were not uniform. Thus Rubin *et al.* out of 78 tonsillectomies in children obtained not a single positive culture, though in 3 cases there was a postoperative rise of temperature to over 103°. Cultures were made in all cases with 8 cc. of blood taken preoperatively, within 30 minutes after operation, and 6 and 10 hours postoperatively, so that the series was controlled. Schwarz and Frisch[12] obtained growth in 3 cultures out of 11 taken during tonsillectomy, while cultures made 1 hour preoperatively and 7 hours postoperatively remained sterile. Bartlett and Pratt[2] report 8 positive cultures but fail to state how many cases were excluded "because of contaminants." Wirth[15], in 1932, reported not a single definite positive result in 45 cases, in each of which 6 cultures at varying time intervals were taken. He stated, however, that in a few of the cultures, organisms were obtained which on account of their non-pathogenic nature and sporadic appearance, often after many days of incubation, were considered contaminants. Finally Fischer and Gottdenker[5] in 51 cases report 16 positive cultures. Growth occurred only in 1 of the cultures taken 5 minutes postoperatively, while organisms were recovered with greatest frequency in the 2-hour postoperative cultures. Thus we find complete disagreement both as to the actual occurrence and the time of a bacteremia detectable by blood culture after tonsillectomy.

The recent excellently controlled work of O'Kell and Elliott[9] in which 60.9% of 84 cases showed a transient bacteremia immediately after dental extraction and in which the incidence of positive cultures could be directly correlated with the severity of the dental infection, aroused our interest in the question of posttonsillectomy bacteremia. Whereas O'Kell's demonstration of *S. viridans* bacteremia may be of etiologic significance in cases of subacute bacterial endocarditis, a streptococcal invasion, particularly of the hemolytic type, might explain the recrudescence seen occasionally in cases of glomerulonephritis and rheumatic fever that are subjected to tonsillectomy. Since the bacteremia was transient and came directly after the operative procedure in O'Kell's series and in the work of Barrington and Wright[1] on catheter fever, we decided to take our postoperative cultures as soon as possible after the operation.

Cases. Cultures were made in 22 cases in which tonsillectomy was performed by one of us (C. F.). None of the patients were very young children, the youngest being 7 years and the average 21 years of age. The patients included 4 cases of glomerulonephritis, 2 of rheumatic fever, 3 of infectious arthritis, 1 of uveitis and 8 with a definite history of recurring sore throats. All tonsillectomies were performed by semisharp dissection with scissors under gas, oxygen and ether anesthesia.

Technique. In each case a preliminary blood culture was made preoperatively just after adequate anesthesia was induced and a second culture was made within 5 minutes of the completion of the operation (usually 2 to 3 minutes after removal of mouth gag). For each culture 10 to 15 cc. of blood was withdrawn from an antecubital vein under strictly aseptic technique after preparation of the skin with iodine and alcohol. The blood was injected directly into a warmed flask of unbuffered beef infusion broth with 1% neopeptone and 0.05% dextrose and then incubated at 37° C. The flasks were observed daily for possible growth and as soon as any clouding appeared were opened and 4 to 5 drops removed with sterile pipette for streaking on a blood agar plate and for a stained smear. The original flasks were kept and observed for 21 days. Unfortunately, it was found that the blood-inoculated broth turned cloudy after 4 to 7 days even though sterile. After this had occurred, the flasks were opened and subcultured as above described every 3 to 4 days up to the 14th day and then again on the 21st day. This was done to make certain that no organism produced a transient growth under cover of the cloudiness of the broth and then died off without detection. When a subculture was positive it was immediately repeated and if the result was duplicated the original culture was considered positive. All positive results were further confirmed by direct stained smears and in none did growth fail to persist a full 7 days. Organisms obtained were identified by the standard procedures of the Biological Division. Anaërobic cultures were not attempted because organisms requiring such conditions are not usual in the tonsils and it was O'Kell's experience in his dental cases that a greater number of positive results was obtained by aërobic than by anaërobic methods. In each case the tonsils were saved and cultured. This was done by scalding them in boiling water to kill surface organisms and then by grinding them under aseptic conditions in a sterile mortar with sand and saline. Cultures were made from this material both by streaking on blood agar and by inoculating and pouring a blood agar plate. The streak and pour plates thus obtained were incubated for 48 hours so that in addition to the rapidly growing flora any minute beta hemolytic streptococci present could be identified.[6]

Results. An outline of the individual cases and the results that were obtained is shown in Table 1. Blood from 15 of the 22 cases showed no growth in either preoperative or postoperative cultures at the end of 21 days. In 3 cases, there was growth in the preoperative culture alone, but in 2 of these the growth did not appear until

TABLE 1.—ANALYSIS OF RESULTS.

Case No.	Initials.	Age.	Preoperative culture.	Postoperative culture.	Tonsil cultures.						Reason for tonsillectomy.	Max. Postop. temp.	Clin. flareup.	Length of follow-up.
					B. strep. (%).	Minute B. strep. (%).	Strep. A and G (%).	Staph. aureus (%).	H. infl. (%).	Pneu. (%).				
1	H. S.	16	0	0	..	..	35	30	25	..	Sore throat	100.2	0	7 mos.
2	M. T.	25	0	0	..	1	30	..	35	1	Infectious arthritis	100.0	0	6 mos.
3	C. P.	21	0	0	..	..	25	5	40	..	Peritonsillar abscess, history	99.4	0	5 mos.
4	M. J.	13	0	0	..	10	25	40	...	..	Rheu. ht. dis., active	99.8	0	6½ mos.
5	G. G.	32	0	0	..	5	10	20	40	..	Infectious arthritis	...	?	8 days
6	C. McC.	15	0	0	..	.	5	..	45	..	Advised by school	100.2	0	4 mos.
7	K. G.	13	*B. subtilis* on 19th day at 5th opening	0	..	..	..	..	..	..	Sore throat history	100.2	?	3 days
8	F. J.	7	0	0	20	..	.	..	..	10	Advised by school	100.2	?	2 days
9	M. P.	28	*M. tetragenus* on 15th day at 3d opening	0	5	..	40	..	..	..	Sore throat history	100.2	?	7 days
10	G. C.	20	0	0	25	..	..	50	15	..	Sore throat history	100.4	?	2 days
11	J. Z.	17	0	0	20	..	.	..	70	..	Chr. glomerulonephr.	100.6	Minimal	6 wks.
12	P. T.	14	0	*S. albus* on 23d day at 6th opening	20	..	.	30	..	20	?Rheum. ht. disease, active	101.4	0	5 mos.
13	D. F.	37	0	0	..	..	5	..	20	30	Chronic tonsillitis	99.4	0	10 wks.
14	C. M.	27	0	0	..	..		70			Chest cold, history	99.4	?	3 days
15	W. J.	18	0	0	30	..	30	..	.	.	Acute glomeruloneph., acute onset	104.6	Mild	6 wks.
16	M. M.	21	0	0	..	..	60	30	10	..	Infectious arthritis	99.8	?	2 days
17	W. B.	19	0	*S. aureus* on 11th day at 3d opening	..	20	..	80		..	Uveitis	100.0	?	7 days
18	D. T.	10	0	*H. influenzæ* on 21st day at 4th opening	70	10	..	20	.	..	Ac. glomerulonephr., acute onset	101.0	0	2 mos.
19	M. S.	41	0	0	70	..	20	..	.	..	Ac. glomerulonephr.	101.2	Definite	24 days
20	E. C.	27	Diphtheriod, 6th day, 1st opening	0	..	..	60	15	..	..	Sore throat history	99.8	?	3 days
21	J. K.	36	0	0	80	..	..	..	..	..	Sinusitis history	100.6	?	2 days
22	D. W.	9	0	*S. aureus* on 3d day at 1st opening	35	..	..	5	..	..	Sore throat history	101.0	?	1 day

late (Case 7 a *B. subtilis* on the 19th day at the 5th opening of the flask, Case 9 a *M. tetragenus* on the 15th day at the 3d opening) and it is probable that these were contaminants accidentally introduced at the previous openings of the flask. One preoperative culture (Case 20) yielded an organism with reasonable promptitude (on the 6th day at the 1st opening), but this proved to be a diphtheroid and may well have been a contaminant introduced when the blood culture was taken.

In 4 cases there was growth in the postoperative culture alone. The organisms in 3 of these (Case 12 a *S. albus* on the 23d day at the 6th opening, Case 18 a *H. influenzæ* on the 21st day at the 4th opening, and Case 17 a *S. aureus* on the 11th day at the 3d opening) may have been contaminants accidentally introduced at previous openings of the flask, though the *Hemophilus influenzæ* is such an unusual air-borne contaminant that it may have been present from the beginning and have grown out very slowly to appear on the 21st day. In the 4th postoperative culture (Case 22 a *S. aureus* on the 3d day at the 1st opening) the growth was undoubtedly primary, though the organism may of course have been a contaminant at the time of blood letting. No case gave positive results in both preoperative and postoperative cultures.

An attempt was made to correlate the type of organism obtained on postoperative blood culture with that obtained from the tonsils. Case 17 with a *S. aureus* in the blood (11th day) had 80% *S. aureus* in the tonsils, and Case 22 with a *S. aureus* in the blood (3d day) had less than 5% of this organism in the tonsils. The other 2 postoperative growths (Case 12 with a *S. albus* and Case 18 with a *H. influenzæ*) did not show these organisms on tonsil culture, and the same was true of all the preoperative positive results.

A study of the postoperative courses of the cases was made. The only patient to have a significant febrile rise after operation (Case 15 with temperature of 104.6° 24 hours postoperatively) had entirely negative blood cultures. Of the other 4 whose temperatures rose to 101° to 101.4°, 2 (Cases 18 and 22) had a positive postoperative culture. Of the 4 cases of glomerulonephritis, 3 had flareups of their disease, 1 minimal, 1 mild, and 1 quite definite with a rise in nonprotein nitrogen, but the only one with a positive culture (Case 18 with a *H. influenzæ*) was the one having no flareup. Neither of the 2 cases of rheumatic fever showed a clinical recrudescence, though in 1 (Case 12) a *S. albus* appeared in the postoperative culture on the 23d day. Of the 3 cases of rheumatoid arthritis, adequate follow up was obtained on only 1 and that patient had no flareup; in all 3 the blood culture remained sterile.

Discussion. It is to be remembered that the technique of blood culture, in which 10 to 15 cc. of blood is withdrawn, representing only a relatively minute portion of the total blood volume, is a fairly crude method for determining slight and transient bacteremia. But interpretation must be made in the light of its results. In our cases this depends entirely on whether the few positive cultures which were obtained, represented true bacteremias or merely contaminations. This cannot be definitely determined. The technique employed necessitated such frequent subcultures (a total of 123 flask openings during the work) that the risk of contamination was unavoidable. But at least one of the organisms (*H. influenzæ*) was not a usual air-borne bacterium. The attempt to correlate the organisms found in blood cultures with those in the tonsils was successful in but 50% of the postoperative and in none of the preoperative cultures. But inasmuch as tonsillectomy is not carried out in a sterile field this confirmation could not be as rigorously demanded as in Seifert's cases in which an abscess was aseptically incised. The three factors which suggest most strongly that some of the positive results were contaminants are first, the late appearance of the growth, in several instances, of an organism which normally grows out rapidly in culture; second, the observation that the positive results were obtained in nearly as many preoperative as postoperative cases; and third, that when positive results were obtained they were never found in both cultures from the same patient. Obviously, however, the series is too small to permit one to draw valid statistical conclusions.

Since our results hinge on whether or not the positive cultures are thought due to contaminants, it is natural to consider if the disagreement between the other published reports is not due to differences in this interpretation, as well as to the more obvious differences in technique. Certainly the disagreement is a fundamental one and applies as well to cultures in other conditions. Thus Cecil, Nicholls and Stainsby[3] reported they had recovered organisms by prolonged culturing of blood from 61.5% of patients with rheumatoid arthritis, while several subsequent observers [4,7,8,14] have been unable to repeat this. Although it is generally believed that the blood stream of healthy individuals is sterile, there are several reports, such as that of Reith and Squier,[10] in which the observers claim to have obtained growth in a moderate proportion of entirely normal persons. For a solution of this controversy it would seem advisable: (1) that the technique of culturing be described in full detail in all protocols (as has been attempted above); and, (2) that all positive results be recorded as such, together with the reasons for and against considering them as contaminants. Meanwhile because of the conflicting reports in the literature and the paucity of our own results we feel that the existence of a blood-stream invasion in a significant number of cases following tonsillectomy has not been established.

It is of interest that a technique very similar to that employed here, when applied to a case of rheumatic heart disease (J. H. H.

65406) undergoing extensive dental extractions, resulted in a growth of *S. viridans* from the blood stream on two occasions. Both times growth occurred in the culture made 5 minutes after the extraction, whereas subsequent cultures and 1 preoperative culture remained sterile. This is in agreement with the results of O'Kell and Elliott.[9] It is obvious, however, that in the extraction of periapically infected teeth, as well as in the incision and drainage of abscesses, a purulent focus may be opened to the blood stream, while in the dissection of chronically infected tonsils such an occurrence would be unusual. This difference probably accounts for the divergent results in these two types of cases.

Conclusions. 1. Of 22 patients in whom tonsillectomy was performed and from whom preoperative and postoperative blood cultures were taken, 4 (18.2%) showed growth in the postoperative culture and 3 (13.6%) showed growth in the preoperative culture.

2. Whether these positive cultures represented true blood-stream invaders is doubtful in most of the cases and it is to be remarked that the preoperative growths were nearly as numerous as the postoperative ones, and that in no case was there growth both preoperatively and postoperatively in the same patient.

3. No constant relation could be made out between the clinical course and the presence or absence of a positive culture.

4. It is suggested that the discrepancy between the results of those who have already written on this subject is due to differences both in technique and in interpretation.

5. The authors feel that the evidence so far (both from their own series of cultures and those in the literature), does not establish the fact that a bacteremia occurs in any significant number of cases after tonsillectomy.

6. As possible explanation of the difference in the results following dental extraction and those after tonsillectomy, it is pointed out that in the former a purulent focus may be opened to the blood-stream while in the latter such an occurrence would be unusual.

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OXYGEN WANT AND INTRACRANIAL PRESSURE.

A Preliminary Report.

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The syndrome of increased intracranial pressure is well known to the clinician. Its clinical diagnosis is reasonably certain in the presence of the following major manifestations: headache, together with projectile vomiting, disturbances of respiration and pulse rate, yawning and sighing, impairment of thought, mental dullness, and possibly unconsciousness with or without changes of the fundus oculi. Its presence in certain conditions, such as intracranial neoplasms, meningitis, intracranial hemorrhage, skull fracture, is undoubted, and it was formerly believed that the limits of its occurrence were well defined by such illnesses. More recently the view has developed that increased intracranial pressure may be present in more transitory states and thus may have a wider clinical importance than was previously believed to be the case.

The number of pathologic states leading to anoxemia is large; pneumonia, severe and acute anemia, and general intoxications as well as failure of circulation generally and locally, are the most prominent, but undoubtedly there are others which as yet have not been recognized in this light.

The following report deals with some of the symptoms produced by experimental induction of anoxemia especially in order to call attention to the appearance of the clinical syndrome typical of increased intracranial pressure as a manifestation of oxygen want.

Method. The experiments took place in a chamber and were carried out in association with D. B. Dill.[4] The subjects were members of the laboratory staff. The oxygen tension in the chamber was gradually lowered and kept so as to correspond to an altitude varying between 15,500 and 17,000 feet, the partial pressure of oxygen being lowered by addition of nitrogen. The subjects stayed in this chamber 4 to 7 hours. Data regarding the circulation, respiration and other factors were obtained once before the atmospheric O_2 tension had been reduced, and on 2 or 3 separate occasions during the experiment. The oxygen saturation of the blood of the subjects during the stay in the chamber varied in different persons between approximately 50 and 70%, whereas the atmospheric O_2 tension was reduced to the same degree for all individuals.

Almost all of our subjects who were exposed to low-oxygen pressure after approximately 2 hours complained of headaches. Headache, together with other neurologic symptoms as ataxia, muscular weakness, mental changes, has been described by Barcroft[2] and Haldane.[6] But we noticed that the headache resulting from the anoxic state artificially produced became much more severe immediately the subject breathed an atmosphere with a sufficient complement of oxygen to raise the arterial saturation to the normal level. This headache persisted for 2 to 6 hours, gradually diminishing during the last one or two until it completely disappeared. It was refractory to the usual analgetics such as aspirin and pyramidon. The effect of position is variable, but in most cases the headache is aggravated by lowering the head.

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Also in the majority of our subjects, and mostly after the onset of the headache, repeated or even continuous yawning and sighing was observed. A dilatation of the retinal veins beginning early during the anoxic state preceding headache, yawning, and sighing has been seen by one of us (J. M.) in 3 of the subjects. The most severe—and significant—manifestations, however, have been observed on 2 other subjects, the authors.

Case J. M.—Four hours after the conclusion of the experiment, during which slight headache was felt, there appeared very severe headache of an intensity never before experienced, projectile vomiting and slow pulse. Vomiting occurred 3 times; the pulse rate was 52 to 56 beats per minute, the normal pulse rate in this individual being around 80 beats per minute.

Case J. W. T.—About 4 hours after the beginning of the experiment a note was taken by this subject in which there is the first mention of headache, "bad, splitting, parietal, frontal and around the ears." Thereafter the headache remained constant, until the full complement of oxygen was breathed at which time the headache was greatly aggravated. Five minutes after leaving the chamber the headache was agonizing and at that time projectile vomiting occurred. An excerpt from the notes of the physician who took charge of the subject after leaving the chamber reads as follows: "Heart rate slow, 40, regular. Sounds of good quality. Respirations regular, shallow, at times almost imperceptible. Artificial respiration at frequent intervals." The mental state of this subject following the anoxemia was characterized by a stuporous condition in which volition was at a minimum, although perception and memory did not seem significantly impaired. A more complete report of the mental condition of this subject will appear elsewhere.

Although in neurologic conditions headache alone often is a general sign of increased intracranial pressure and yawning and sighing a significant evidence of medullary compression, we do not as yet feel certain enough to make a general statement as to the underlying pathologic occurrences in those of our subjects who showed these symptoms. But we believe that in the presence of headache, together with projectile vomiting and slow pulse rate or even of these three symptoms combined with semiconsciousness disturbances of respiration and mental impairment as observed in the case of J. M. and J. W. T., the diagnosis of increased intracranial pressure is justified. Actual proof of the evidence of high intracranial pressure must await direct measurements both in the cases when the clinical syndrome is complete and those where headache, yawning, sighing, and dilatation of the retinal veins appear as the only manifestations. Unfortunately, ophthalmoscopic examinations were not carried out during the illness of J. W. T. and J. M. above mentioned. Observations of the pressure by lumbar puncture would have yielded the clearest results, but some danger would have been incurred under the conditions of our experiments. One of us is now endeavoring to arrive at the same measurements indirectly by applying the ophthalmodynamometric technique introduced by Baillart,[1] Baurmann,[3] and Sobanski.[9]

Collateral evidence would tend to support the concept of there being an increase in the intracranial pressure during anoxemia. Forbes, Cobb and Fremont-Smith[5] were able to show an elevation in the intracranial pressure as a result of CO poisoning. Furthermore, it has been demonstrated by Landis[7] that the rate of capillary filtration is increased by oxygen lack. Increased capillary permeability being one of the important causes leading to swelling everywhere in the body, we are now seeking evidence showing how far an increase in the volume of the brain itself (brain swelling according to Reichardt[8]) may play a rôle in producing the increase of intracranial pressure following anoxemia. Other factors such as abnormalities of intracranial circulation, especially of the veins and disturbances in secretion and absorption of the cerebrospinal fluid, may also be involved in this problem.

Furthermore, the question arises why different individuals react to such a varying degree that some may be severely sick and endangered while others show just a few symptoms under the same circumstances. There may be some relationship between the amount of oxygen supplied to the brain tissue and the severity of the sickness during or after exposure to a low atmospheric oxygen tension. J. W. T., for instance, who showed the most severe symptoms, had the lowest oxygen saturation in his arterial blood we have observed in our subjects; on the other hand, J. M., having been very ill, although to a lesser degree, had an average saturation. But the saturation of the arterial blood is only one factor on which the oxygen tension in the brain depends. Rate of blood flow and metabolism have to be considered in any attempt to find a quantitative relationship between oxygen want and severity of the neurologic symptoms.

All these questions are not only of interest in our special field; they deserve the attention of the neurologist and neurosurgeon studying the mechanism of the increase of intracranial pressure. They claim the interest of everyone who sees the various cerebral manifestations in clinical cases of anoxemia, produced, for instance, by pneumonia. Therefore, we trust that this short communication may draw the attention of clinicians to the symptoms of increased intracranial pressure following anoxemia, so that the problem can be attacked on a broader basis.

Summary. 1. Clinical manifestations of increased intracranial pressure following exposure to low atmospheric oxygen tension are reported.

2. The response of individuals exposed to low-oxygen tension may vary from mild to severe headache, yawning and sighing, on the one hand, to severe physical and mental aberrations characterized by excruciating headache, projectile vomiting, bradycardia, superficial respiration and semiconsciousness, on the other.

3. The possible mechanism of the increase in intracranial pressure following anoxemia is briefly discussed and the necessity of further study of the particular rôle of brain swelling, besides spinal fluid mechanics and blood circulation pointed out.

4. The oxygen saturation of the arterial blood of different persons exposed to low oxygen is different under the same circumstances. Furthermore, the reduction of the oxygen saturation of arterial blood seems to have no quantitative relationship to the severity of the clinical manifestations; other factors influencing the oxygen tension in the brain itself, such as rate of blood flow and metabolic rate, may play a rôle.

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THE CONTROL OF GASTRIC ACIDITY IN PEPTIC ULCER BY ALKALINIZED POWDERED SKIMMED MILK TABLETS.*

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Ideally, the control of the gastric acidity by alkalies should be highly individualized for each patient with peptic ulcer. However, it is appreciated that the frequent assay of the stomach contents to insure this control is not always possible. For this reason it seems desirable to know what methods are most efficient in reducing the corrosive action of the gastric juice.

In previous communications[1,2a,b] an attempt has been made to show that a simplification of a standardized Sippy regimen is possible. An effort has been made to show that there need be no reduction of efficiency in the neutralization of the gastric acidity even when the number of feedings are reduced by one-half. This is

* This study was aided by a grant from The Upjohn Company, Kalamazoo, Mich.

true when powdered whole milk is substituted for milk and cream. A slightly greater efficiency has been noted when the usual amount of sodium bicarbonate is decreased, which was not found to be true when the sodium bicarbonate was omitted altogether. Of the many combinations of alkalies pressed into tablets of powdered whole milk that were tested, a mixture of 12.5 gm. of powdered whole milk, 0.6 gm. of sodium bicarbonate and 2 gm. of calcium carbonate has been found to be a good, though not a perfect, neutralizing agent.

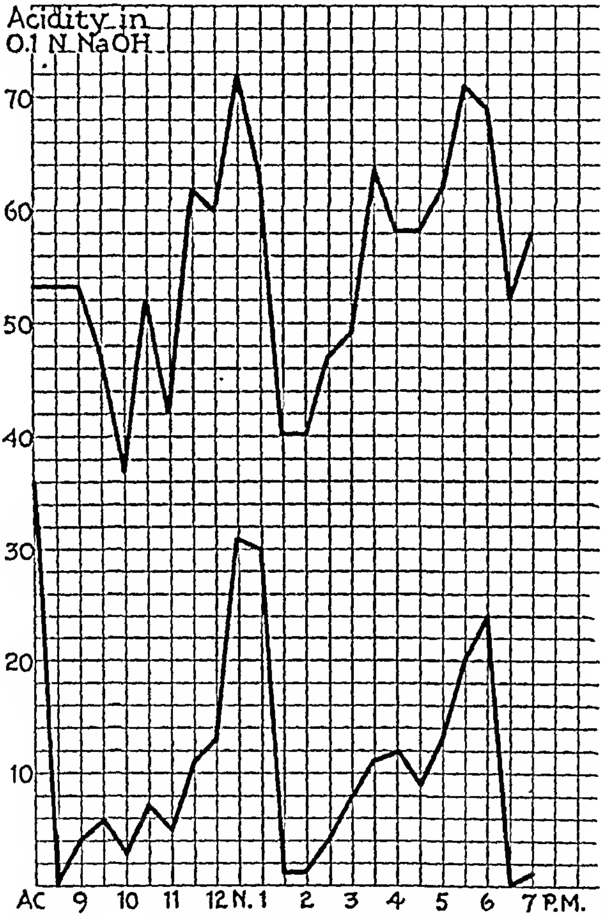

FIG. 1.—Routine Sippy regimen. Average free and total acid curves on 13 patients receiving 90 cc. of milk and cream on the hour and 20 gm. sod. bicarb. and 0.6 gm. calc. carb. on the half hour.

In this present paper it is proposed to show that a larger percentage of patients show an adequate control of hydrochloric acid when powdered skimmed milk tablets are used instead of powdered whole milk, when the amount of alkali is not varied.

Material and Data. Thirteen of the same patients were used for this study who were employed and reported previously.[1] All were male patients with peptic ulcer from the Medical Clinic of Northwestern University Medical School. Meals were served at Passavant Memorial Hospital and consisted of the usual foods permitted on fourth week Sippy management. Milk and cream and powders or tablets were given as interval feedings. Aspirations were performed at half-hourly periods.

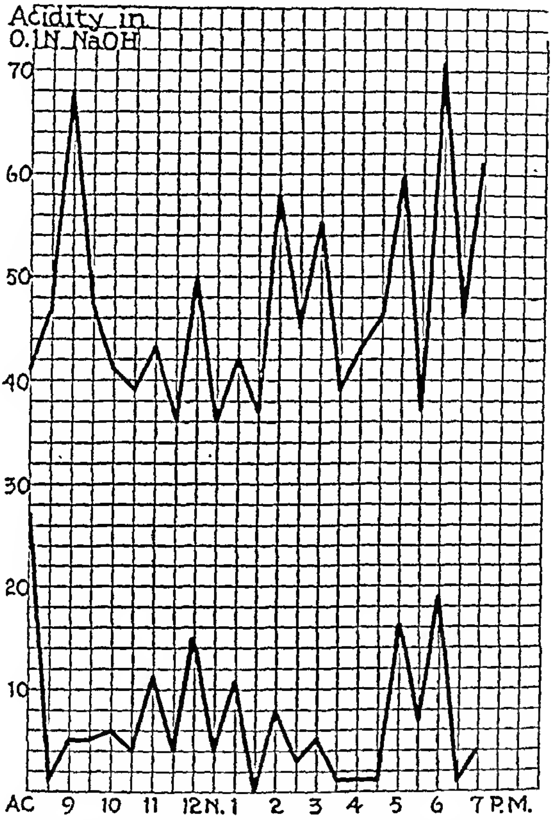

Fig. 2.—Sippy powders with powdered whole milk. Average free and total acid curves on 13 patients receiving 12.5 gm. powdered whole milk (28% butterfat), 2 gm. sod. bicarb. and 0.6 gm. calc. carb. on the hour in 4 tablets with 90 cc. water. The half-hour feeding was omitted.

As a standard for comparison, the results obtained with a routine Sippy management may be seen on Figure 1. These are the average acid curves obtained on the 13 patients in the present series. The titrated total acid values are seen to vary roughly between 40 and 70 clinical units. The free acid curve following the total is seen to descend sharply 3 times daily immediately following the meals allowed. In spite of the milk and cream (90 cc.) each hour allowed on the hour and the routine Sippy powder (2 gm. sodium bicarbonate and 0.6 gm. calcium carbonate) allowed on the half-hour, the acid values increase steadily until at noon the average free acidity almost equals the fasting values aspirated at 8 A.M. Again, before the evening meal, a peak of 24 clinical units of free acidity is reached.

In Figure 2 the effect of the same amount of alkali with powdered whole milk is considered on the same patients. The difference between Figure 2 and Figure 1 is: 1, That powdered whole milk (12.5 gm.) was substituted for the milk and cream feedings on the hour; 2, that the same amount of alkali (2 gm. sodium bicarbonate and 0.6 gm. calcium carbonate) was mixed with the powdered whole milk and administered in the form of tablets; and 3, that the half-hour feedings were omitted, although the aspirations were not. Ninety cc. of water was taken with the tablets. Figure 2 shows that while the extremes of the total acid curve is seen to vary between 40 and 70 clinical units, on the whole the values are slightly lower. The neutralization of the free acid, likewise, was not perfect,

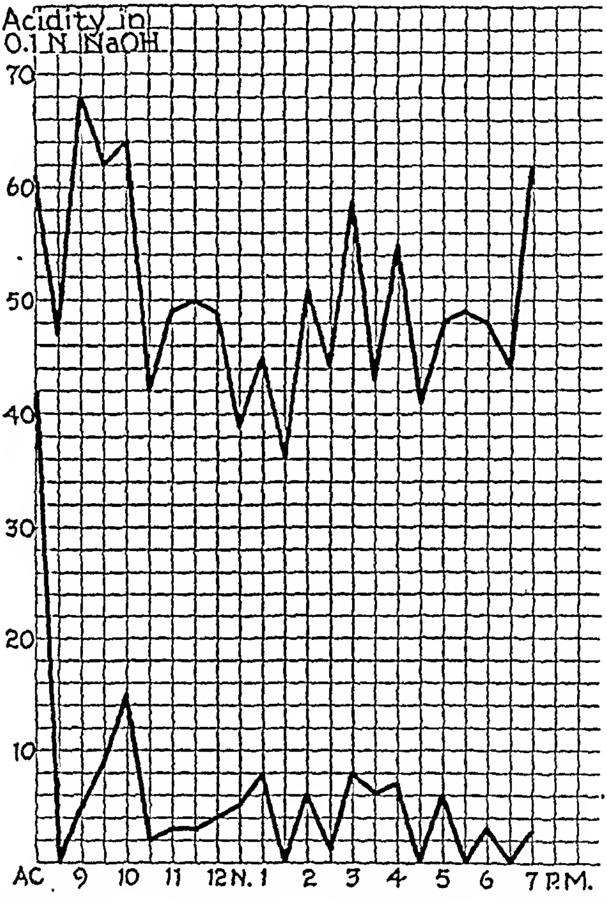

FIG. 3.—Alkalinized powdered whole milk tablets. Average free and total acid curves on 13 patients receiving 12.5 gm. powdered whole milk (28% butterfat), 0.6 gm. sod. bicarb. and 2 gm. calc. carb. on the hour in 4 tablets with 90 cc. water. The half-hour feeding was omitted.

as the curve shows. However, high peaks were not reached before meals in the same manner that was noted with the routine Sippy procedure.

Figure 3 shows the average of the free and the total acid determinations on the same patients when the half-hour feedings were omitted. The feedings given every hour consisted of 4 tablets that were made of whole powdered milk (12.5 gm.), but the amount of alkali was changed so that each hourly dose contained 2 gm. calcium carbonate and 0.6 gm. sodium bicarbonate. The total acid curve is seen to be lower than when milk and cream is used with a larger amount of sodium bicarbonate, as well as lower than when powdered whole milk is used with a larger amount of sodium bicarbonate. Except for one period at 10 A.M. the average free acid values were no greater than 8 clinical units. This result is not surprising when one considers previously reported figures.[1]

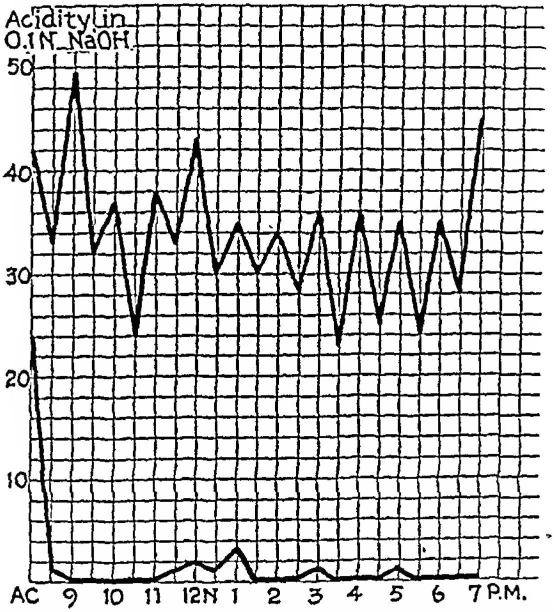

FIG. 4.—Alkalinized powdered skimmed milk tablets. Average free and total curves on 13 patients receiving 12.5 gm. powdered skimmed milk (5% butterfat), 0.6 gm. sod. bicarb. and 2 gm. calc. carb. with 90 cc. water. The half-hour feeding was omitted.

A more complete picture of acid neutralization is seen in Figure 4. The same patients were administered 4 tablets containing the same amount of alkali that was used in the experiments of Figure 3 (2 gm. calcium carbonate and 0.6 gm. sodium bicarbonate). Instead of the powdered whole milk, however, powdered skimmed milk was substituted in their manufacture. The stimulation afforded the gastric secretion, as evidenced by the total acid curve, was far less than when the other preparations were used. At the same time the average free acid curve as plotted for the entire day approaches almost perfect neutralization.

Discussion. It is well appreciated that the number of ambulatory patients with peptic ulcer studied for this report represents a small series. The same patients were used, however, in the 4 experiments. Variations in the amount of acid in stomach contents is well known, but is is assumed here that the 13 patients would not show the same physiologic variations (higher or lower) for the same test. Therefore, the alteration of materials administered must be a major factor in the modification of the present results.

That a routine standardized Sippy regimen leaves much to be desired is plainly shown. The noon acid values are almost at the same peak noted for the fasting specimens. This, in spite of the numerous frequent feedings, as has been pointed out, makes numerous aspirations necessary if complete neutralization is to be the goal. Unfortunately, the present studies could not be continued throughout the night.

The results do show that the frequency of the feedings may be reduced with no sacrifice in the efficiency of the neutralization when substitutions are made in the usual Sippy treatment. Powdered whole milk in the form of alkalinized tablets may thus be substituted for whole milk and cream and alkaline powders. An increase in neutralizing efficacy is also noted with a reduction in the amount of soda bicarbonate. Conjectures on these points are considered elsewhere.

Since effectiveness, as well as cheapness (as regards cost to the patient) is to be considered, it seemed reasonable to try the effect of skimmed milk substituted for the powdered whole milk in the tablets. A skimmed milk with 5% butter fat was used, whereas there was 28% in the whole powdered milk. This reduced the calories from approximately 118 in the milk and cream (90 cc.), 62.5 in the powdered whole milk (12.5 gm.), to 48 in the powdered skimmed milk (12.5 gm.). However, this reduction was not considered a serious objection, for an increase in the calories could be achieved with the meals and especially when the more complete neutralization was noted. The exact reasons for the lower acid values when the powdered skimmed milk tablets were used is not apparent at present.

Summary. In a standardized Sippy regimen 12.5 gm. of powdered skimmed milk was substituted for 90 cc. of milk and cream. The amount of sodium bicarbonate was reduced from 2 to 0.6 gm. and the amount of calcium carbonate increased from 0.6 to 2 gm. This was tested on 13 peptic ulcer patients and compared with the results of several other diets previously studied on these same patients.

This material, given once an hour in the form of tablets in addition to the three meals, resulted in a more complete neutralization of the gastric acidity than could be obtained with the routine Sippy procedure and the modifications tried.

Miss Helen Gurley gave expert technical assistance.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA.

REPORT OF A CASE AND AN ANALYSIS OF SEVENTEEN PREVIOUSLY REPORTED CASES.

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Subcutaneous emphysema widespread in character following an attack of bronchial asthma presents so alarming a picture that despite its rarity, its course and prognosis should be more widely known than at present. Considering the frequency of severe attacks of bronchial asthma, it seems strange that this complication is so rare. We have been able to collect only 17 previous cases from the literature.

Case Report. M. T., female, aged 3 years, was admitted to this hospital, September 11, 1935, with the complaint of extreme dyspnea, swelling of the face, neck, trunk and arms following an attack of bronchial asthma. The previous night she had had an attack of bronchial asthma in no way different than the ones she had had innumerable times before. Toward morning the child seemed critically ill. Her dyspnea became worse and the mother noted progressive swelling of the face and chest.

Three weeks before admission she had her tonsils and adenoids removed, and 2 weeks later developed an upper respiratory infection. She had eczema in infancy and bronchial asthma before the age of one year. Her mother suffered from a severe form of bronchial asthma for many years. The patient's general health had been good except for frequent colds. There was a history of food sensitivity in infancy for which desensitization was said to have been attempted.

Physical examination showed a well-developed girl of 3 years, acutely ill, markedly dyspneic with breathing approaching the Kussmaul type. There were bubbling sounds audible from the mucus in the throat. The breath had a fruity odor suggestive of ketosis. Her face was flushed and swollen, being puffier on the right side than the left. The right eye was

TABLE 1.—CASES OF SUBCUTANEOUS EMPHYSEMA COMPLICATIVE BRONCHIAL ASTHMA.

Author.	Age (yrs.)	Sex.	Duration of asthma.	Location of emphysema.	Duration of emphysema (days).
1. Knott,[11] 1850	5	F	Not given	Above sternum spreading lat. and inf. to post. inf. triangle of neck and sup. half of sternum	21
2. Watson,[19] 1885	18	F	Since childhood	Right side of neck and right ant. chest to upper margin of breast	9
3. Calverly,[4] 1899	17	M	11 yrs.	Neck just above clavicles; ant. and post. triangles of neck reaching to level of jaw lat. and ant. as high as thyroid cartilage.	4
4. Whitby,[20] 1905	25	M	Since boyhood	Front and sides of neck; face as far as lower part of forehead, both arms as far as wrist, front of thorax and back as far as upper border of sacrum	The emphysema disappeared gradually.
5. Kahn,[8] 1927	8	F	6 yrs.	Upper part of chest and back, both shoulders, neck, both sides of lower face	10
6. MacDermott[13] 1929	22	M	6 yrs.	Neck, to angle of jaw and just below clavicles	5–6
7. Scheltema,[16] 1931	30	M	First attack	Half the body; face closing, eyes completely and spreading down arms.	7
8. Artagaveytia and Zanzi[1] 1932	18	M	Since infancy	Right side of chest, the neck, over clavicles, eyelids, both upper limbs, except 4 fingers of left hand; inguinal region	8
9. Seremini and Berro,[17] 1932	Not given	F (young)	Not given	Chest and neck	"Few"
10. Mourigan and Cervino,[14] 1932	21	F	Since childhood	Neck, right side of chest, right arm	2
11. Kruysveldt,[12] 1933	22	F	Attacks of shortness of breath since childhood	Entire body from eyes to knees, also scalp, forehead	14
12. Davidson,[5] 1934	9	F	8 yrs.	Upper part of chest post., both shoulders, both arms as far as dorsum of hand, angles of jaw, clavicles and both sides of lower lower face; "crackling in ears"	7
13. Pastorino,[15] 1935	7	F	Not given	Neck, right side, upper ant. portion of thorax, a small portion of upper limbs	6–7
14. Pastorino,[15] 1935	14	M	Since childhood	Neck, face, arms, upper extremities to dorsum of hands; abdomen; upper thighs	10
15. Sheldon and Robinson,[18] 1936	16	M	1 yr.	Left ant. thorax from mid. to post. axillary line, left upper quadrant of abdomen, axilla and ant. and post. triangle of left side of neck	4
16. Kirsner,[10] 1937	38	M	First attack	Face, supraclavicular region, both arms to dorsum of hand	20
17. Bridges,[3] 1937	6	M	3 yrs	Face, ant. and post. triangles of neck, pectoral regions	6
18. Rosenberg and Rosenberg 1938	3	F	Prior to 1 yr. of age	Neck, face, upper extremities, chest, upper abdomen	12

partially closed (Fig. 1). Both eyelids were puffy; the pupils were wide and reacted well to light. The cornea and conjunctivæ were clear. There was extensive subcutaneous emphysema involving the forehead, face, neck, thorax, upper part of abdomen and the arms down to the wrists. Crepitus was easily demonstrated. On the anterior abdominal wall, the emphysema was present only to about the level of the umbilicus.

Auscultation of the chest revealed coarse râles, sonorous and sibilant squeaks audible through the overlying crepitant râles produced by the presence of air in the subcutaneous tissues. The throat was diffusely red and had a glazed appearance; the pharynx was covered with a tenacious stringy mucus. There were dried crusts in the nose. The heart sounds were distant and the rate was rapid and regular.

Roentgen ray on admission (Figs. 2 to 4) showed a marked amount of air in the soft parts about the neck, chest and abdomen. There was spotty density throughout both lung fields, with an area of considerable density in the right upper lobe. The trachea was displaced somewhat to the right. The diaphragm was not elevated. In the lateral view of the chest, the anterior border of the heart was well separated from the anterior chest wall. The area of density in the right upper lobe was considered to be due to atelectasis. About 1 week after admission, September 17, 1935, Roentgen ray (Fig. 5) showed less air in the soft parts about the neck, chest and abdomen. The chest as a whole was clearer than on the previous examination.

Urine examination showed no sugar or albumin but there was a 3+ acetone present. The white blood count was 12,960 with polys, 77%; lymphocytes, 14%; eosinophils, 8%; basophils, 1%. The red blood count was 5,500,000 with 95% hemoglobin. The intradermal tuberculin test was negative with 0.01 mg. and 0.1 mg. The temperatures was never above 100° F.

She was given forced fluids of high carbohydrate content and the usual therapy for bronchial asthma, adrenalin chloride 1:1000 by hypodermic. No attempt was made to treat her subcutaneous emphysema. The alarming nature of her condition persisted for about 12 hours after admission. She improved from her asthmatic attack in the course of a day or so but the subcutaneous emphysema remained for over a week. She was discharged from the hospital, September 18, 1935.

During the past 2 years since the onset of this complication, the child has had 6 or more severe attacks of bronchial asthma with no recurrence of the subcutaneous emphysema.

Comment. In most of the cases reported in the literature, the presence of widespread subcutaneous emphysema complicating an attack of bronchial asthma, produced an alarming picture. In some cases (Kruyseveldt and our case), the dyspnea was so severe and the general condition so alarming that exodus seemed a possibility. Yet uneventful recovery ensued in these and all the other cases recorded.

The pathogenesis of subcutaneous emphysema has been adequately discussed by Artagaveytia and Zanzi,[1] Gallinek,[6] and Berkley and Coffen.[2] Animal experimentation conducted by Kelman,[9] and Joannides and Tsoulos[7] confirms the generally accepted view that the air escapes from one or more ruptured lung vesicles and spreads by way of the root of the lung to the superior

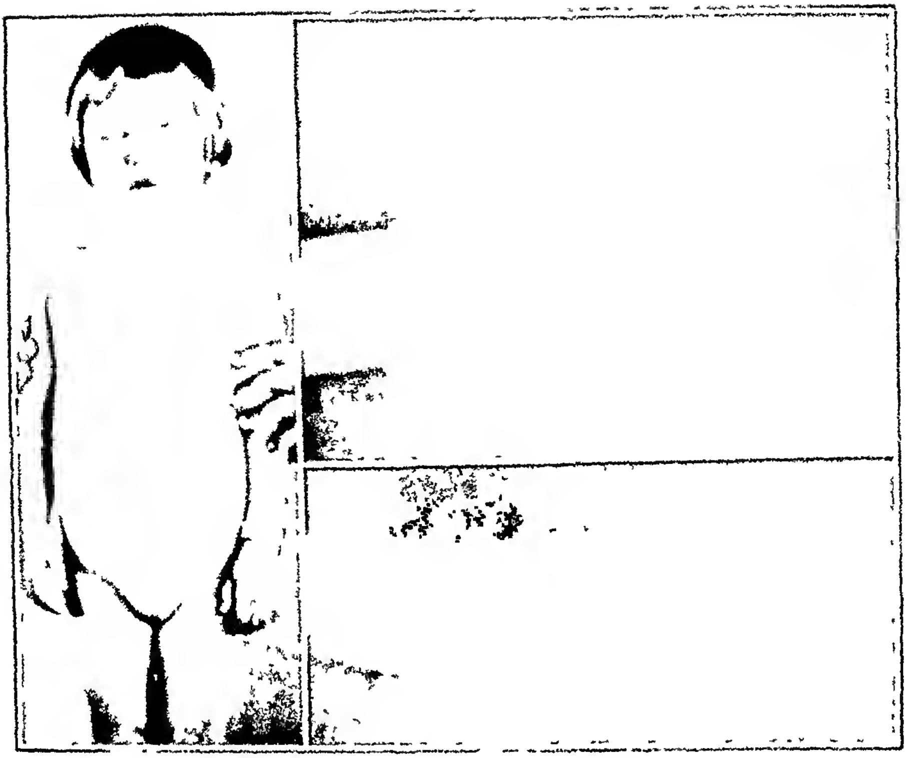

Fig. 1 Fig. 2

Fig. 1.—September 12, 1935. [illegible] of the right eye, swelling of the face, neck, thorax and abdomen.

Fig. 2.—September 11, 1935. A, [illegible] air in the left forearm. B, [illegible] air in the right forearm.

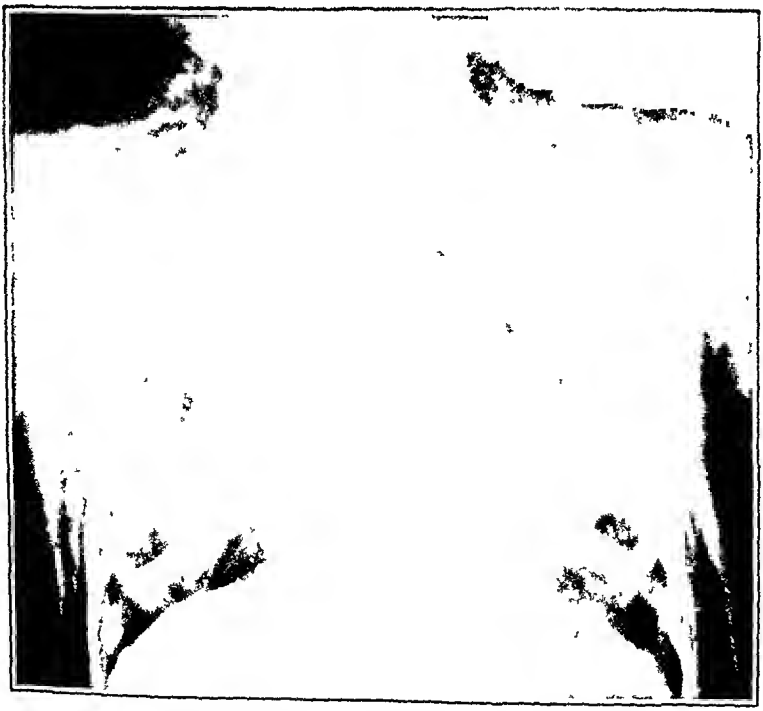

Fig. 3.—September 11, 1935. Anteroposterior view showing marked subcutaneous emphysema of the neck, thoracic wall and upper abdominal wall.

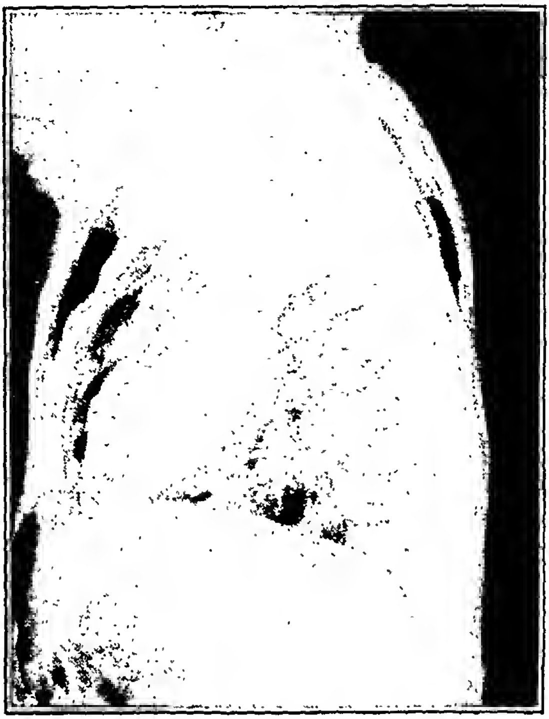

Fig. 4.—September 11, 1935. Lateral view showing subcutaneous emphysema of the anterior chest wall and back.

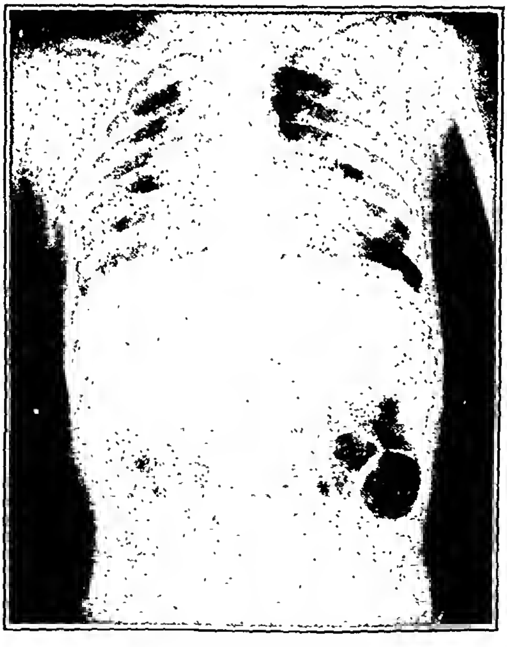

Fig. 5.—September 17, 1935. Anteropostero view showing gradual absorption of the imprisoned air.

mediastinum and neck and thence along fascial planes to the trunk and upper extremities.

Clinically, the subcutaneous emphysema began in the neck in practically all the cases, spread to the face, the upper extremities, the thorax, abdomen and rarely to the thighs (Pastorino,[15] Kruysveldt[12]). In only 2 cases (Scheltema,[16] Kirsner[10]) did the emphysema occur in the first asthmatic attack. All the others regardless of age had had several, often innumerable previous attacks of asthma without complication. The youngest case was our own, a girl aged 3 years, and the oldest, 38 years (Kirsner[10]). Practically all the patients were young individuals: 6 in the first decade of life, 5 in the second, 4 in the third and 2 in the fourth. In 1 case no age was given but the patient was described as a "young female." There was equal division of the sex incidence, half the individuals being male and half female. There have been no recurrences of subcutaneous emphysema despite frequent subsequent attacks of the bronchial asthma.

The shortest duration of the emphysema was 2 days (Mourigan and Cervino[14]) and the longest 3 weeks (Knott[11]), with an average duration of from 7 to 10 days. Knott's case is worthy of special comment. It was not reported by him in the year 1850 as complicating bronchial asthma but his description of a cough with "sonorous and sibilant rhonchi" seems sufficient to include his case in this series.

No other treatment than that of the bronchial asthma itself was employed in any of the cases with the single exception of Kirsner's patient in whom a needle was inserted for release of the imprisoned air.

Conclusions. 1. A case of widespread subcutaneous emphysema complicating an attack of bronchial asthma is described. The alarming picture this condition presents is stressed and the invariably good prognosis discussed.

2. A series of 17 similar cases collected from the literature is analyzed.

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BOOK REVIEWS AND NOTICES.

A PRACTICAL TREATISE ON DISEASES OF THE SKIN for the Use of Students and Practitioners. By OLIVER S. ORMSBY, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago; Dermatologist to the Presbyterian and St. Anthony's Hospitals, and the Home for Destitute Crippled Children, etc. With revision of the Histopathology and Mycology by CLARK WYLIE FINNERUD, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1334; 658 illustrations, 3 colored plates. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $12.00.

ALL American dermatologists will be glad to see this encyclopedic work by a distinguished author reach its fifth edition. The enormous range of dermatologic phenomena finds here as complete an enumeration as could possibly be expected of even a large one-volume text. The descriptions of disease entities and complexes exhibit the characteristic meticulousness and clarity of the author's writings, and from the more intricate differential material and the therapeutic discussions even the expert can obtain invaluable pointers and slants on one of the largest experiences available in the English language. The photography is excellent, but the illustrations, as in most dermatologic presentations, lean toward extreme and picturesque examples rather than the absolutely characteristic or most frequent lesions.

To those familiar with textbook writing and the problems of succeeding editions, the statement of the publisher that this work, in its present form . . . . "reflects with accuracy the advanced position of present-day dermatology," must be taken with a grain of salt. That the work is intended for the use of practitioners; that it had its foundations laid in more or less unalterable form in the days of morphologic dermatology; that it endeavors to cover a field requiring two separate presentations (dermatology and syphilology), and what amounts to a system rather than a single volume work for either field, these are facts that cannot be evaded. The complete rewriting required for utilization of modern dermatologic advances would be impossible in any revision of an established text with which the Reviewer is familiar. The publishers are therefore to be criticized for allowing exaggerated statements to appear in their advertising. Even a very ordinary review must point out that the physiology of the skin is inadequately presented. The hydrogen-ion concentration of the sweat and the difference between the behavior of apocrine and eccrine sweat glands, for example, is not even mentioned, important though it is for cutaneous etiology. The presentation of allergy, in its relation to cutaneous disease, falls far short of even modest requirements for practical interpretations.

The rewritten section on the cutaneous mycoses, in which this work at first led its field, leaves much to be desired, especially in the field of the intertriginous eruptions. The presentation of syphilis, while modernized on the score of treatment, is not and could not possibly be what the publishers describe as "particularly adequate."

It is, however, an injustice to expect a revision to be a rewriting. For those who, as undergraduate students and as practitioners, desire a dermatologic encyclopedia on conservative lines, with excellent and inclusive differentiation, and an adequate therapy of a more or less empirical type, this work is excellent. J. S.

THE COLLAPSE THERAPY OF PULMONARY TUBERCULOSIS. By JOHN ALEXANDER, B.S., M.A., M.D., F.A.C.S., Professor of Surgery, University of Michigan; Surgeon-in-Charge, Division of Thoracic Surgery, Department of Surgery, University of Michigan Hospital. With Contributions of Chapters III and IV on Physiological Principles and Pathology of Pulmonary Collapse by MAX PINNER, M.D., F.A.C.P., Herman M. Biggs Memorial Hospital, Ithaca, N. Y., etc.; Chapters XI and XII on Pneumothorax by JOHN BLAIR BARNWELL, B.A., M.D., Associate Professor of Internal Medicine, University of Michigan, etc.; Chapter XV on Oleothorax by KIRBY SMITH HOWLETT, JR., M.S., M.D., Resident, Laurel Hills State Tuberculosis Sanatorium, Shelton, Conn. Pp. 705; 367 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price $15.00.

THE value of collapse therapy in the treatment of pulmonary tuberculosis is discussed in an authoritative and convincing manner. There is need for an equally rational and lucid presentation of the medical treatment of pulmonary tuberculosis with an equally critical analysis of principles, indications, methods and results. If such a work is not forthcoming it will certainly appear that only those unfortunate patients whom the surgeon rejects should rely on medical treatment for the control of their disease. The author estimates that between 50 and 85% of patients with pulmonary tuberculosis should receive collapse therapy in some form.

The author has made a splendid choice of collaborators. The chapters on the physiologic principles and pathology of pulmonary collapse are an able and all too brief consideration of a poorly explored subject. A sound discussion of the use of oleothorax is presented and the section on pneumothorax is a model of thoroughness, clarity and good judgment. The chapters dealing with the indications for various surgical procedures are particularly valuable to the physician. It should be recognized, however, that in many sections of the country the use of phrenic nerve paralysis is rapidly diminishing while the value of artificial pneumothorax has been enhanced as a result of improvements in the technique of closed intrapleural pneumonolysis. The author's emphysis on phrenic nerve operations and his sparing approval of the Jacobeus operation should not be considered representative of present opinion.

The volume is attractive, easy to read and the illustrations, including reproductions of roentgenograms are excellent. Since collapse therapy should be carefully considered for every patient with pulmonary tuberculosis, this work is equally important to the physician and to the chest surgeon. Only 50 pages are devoted to technical procedures of purely surgical interest. This book is highly recommended to all who are interested in the treatment of pulmonary tuberculosis. H. H.

DOCTORS ON HORSEBACK. Pioneers of American Medicine. By JAMES THOMAS FLEXNER. Pp. 370; illustrated. New York: The Viking Press, 1937. Price, $2.75.

SEVEN great men have been selected by the author as types of famous American doctors of more than a century ago—"On Horseback," not because they traveled unsettled regions, like our present-day nurses on horseback of the Appalachian Mountains, but presumably because they lived in the horse stage of transportation. Actually the gig supported the seats of some of these 7 rather than a horse's back. From the Revolutionary period, Morgan and Rush are chosen, the one as "Seer and Continental Soldier," the other as "Saint or Scourge." In the pioneer days of the midwest, McDowell appears as a jazzed "Backwoods Galahad," and Drake as "Genius on the Ohio," while Beaumont figures with his living laboratory, St. Martin, under the caption "Two Men and Destiny." "The Death of Pain" affords with Morton and Long the occasion for a spirited rehash of the anesthesia controversy. As a Pennsylvanian, the Reviewer takes legitimate pride in the prominent and creditable part played by his university throughout the narrative.

Like many of its prototypes in the field of fictional biography, this book tells a highly picturesque, lively story that should make it a good seller to medical men unacquainted with the history of their professon and to laymen who enjoy looking behind its scenes. The author, with reportorial skill, has unearthed many little known piquant facts about his subjects and, in the words of the cover advertisement, "in this, his first book, has succeeded in combining the two fields" (*i. e.*, fiction and biography). Criticism of inaccuracies might therefore be regarded as carping, but one cannot but regret the occasional misstatement detected even on casual reading. One wishes, too, that somehow the fictional element had been at least indicated as fiction. Also one cannot but wonder at the hidden conflicts in this promising young author which seem to seek escape in his constant carping at the "upper dog." Disproportionate and therefore misleading emphasis is laid on the seamy side of the medicine of those days. The shortcomings of the successful man are rolled under the tongue with obvious gusto; the "aristocrat" is invariably picked on: Shippen's affairs, though he is not one of the subjects chosen, fill a full quarter of the first two chapters and always to his discredit. Rush, admittedly a complex mixture, too often appears in an unfair and disagreeable light; *inter alia*, he is included as one of the principal supporters of the Conway cabal, though qualified historians have rejected this evaluation.

With the above exceptions, criticism may be wholly favorable. The author has delved to good effect in little known manuscript material and so woven his findings into the framework of narratives written in a clear, straightforward style that vivid, and occasionally moving, pictures hold fast the reader's attention. Rush's and Morgan's greatness still manage to shine through the sordid details of contemporary bickerings; Drake's abiding love for Cincinnati, his adopted city, affords a sympathetic explanation of the tortuous career of that hero of the Mississippi Valley; the contributions of Long and Morton are fairly assayed and the problem rested on what constitutes discovery, while all will agree that "Certainly there is enough credit for two to share it." Who will not be convinced also that the heroes of this book and others like them were "strong men who challenged the impossible and won sometimes against greater odds than any which exist today?" E. K.

TWENTY-FIVE YEARS OF HEALTH PROGRESS. A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company, 1911 to 1935. By LOUIS I. DUBLIN, PH.D., Third Vice-President and Statistician, and ALFRED J. LOTKA, D.SC., Assistant Statistician. With the collaboration of the staff of the Statistical Bureau. Pp. 611; with numerous tables and graphs. New York: Metropolitan Life Insurance Company, 1937.

THE authors present an interesting summary and discussion of health progress in the United States during the priod 1911 to 1935, as evaluated by study of the vital statistics of policyholders, comprising a homogeneous but widely distributed group of some millions of workers and their families. This group differs from the general population of the U. S. Registration area, with which it is compared in considering trends, in being predominatingly urban (over 94%), more evenly distributed as to sex, and a comparatively younger group. The study begins in 1911, when the insurance company started its present Health and Welfare campaign.

One is impressed by the extensive gains in life expectancy following, and certainly at least partly due to, the development of a planned and concerted public health activity. In spite of the World War and the depression, this period shows the addition of almost a decade and a half to the average duration of life. Improvement in death rates may be noted all along the line, except in the "degenerative" diseases developing past middle life. The most striking feature of this health picture, however, has been the rapid decline in tuberculosis mortality with its shift in position from first to seventh place in the list of leading causes of death.

The book considers the causes of death under 9 different disease groups. Detailed statistical tables are given for each group, with consideration by color, sex and age, and comparison of trends among policyholders and general population. Discussion is clear and terse, and attempts are made, usually successfully, to derive logical explanations for trends in each group, graphs being used freely.

Rates in policyholders, as would be expected in the group under consideration, are usually higher than in the general population, but they are tending to reduction at a somewhat more rapid rate and are steadily approaching those of the general population.

The book is a wonderful reservoir of interesting and useful statistical material, well arranged and clearly presented and analyzed, and should prove of great value to students, teachers, and public health workers.

H. S.

MENTAL THERAPY. Studies in Fifty Cases. Vols. I and II. By LOUIS S. LONDON, M.D., formerly Past Assistant Surgeon (R.), United States Public Health Service; Medical Officer, United States Veterans' Bureau; Assistant Physician, Central Islip State Hospital, Central Islip, New York, and Manhattan State Hospital, Ward's Island, New York. Pp. 774; 22 illustrations. New York: Covici Friede, 1937. Price, $12.50 the set.

IN this near-orthodox Freudian work are embodied details which positively restrict its sale. Portions of the subject matter: Part I. Metapsychology: evolution of psychotherapeutics, survey of psychoanalysis, meaning of the dream, psychosexual pathology of the child and psychosexual pathology of the sexual instinct. Part II. Psychogenesis and Psychopathology of the Neuroses: analyses of cases showing hysterical neurosis, cardiac neurosis, gastric neurosis, anxiety neurosis with phobia, compulsive thinking, and a doubter; anxiety neurosis in Œdipus situation, anxiety neurosis and sexual impotence, and compulsion neurosis with castration complex. Part III. Paraphiliac Neuroses: case analyses of homosexual neurosis, transvestism, agrophobia, syphilophobia and satyriasis; psychosexual infantilism; sadism and masochism; studies in fetichism and Lesbian love; latent female homosexuality, and female homosexuality—anxiety neurosis. Part IV. Pathogenesis and Psychotherapy of Borderline Neuroses: cases of obsessional, compulsion and anxiety neuroses, latent male and female homosexuality and schizophrenia. Part V. Psychogenesis and Psychotherapy of Schizophrenia: incipient and advanced cases; mechanism in paranoia and analysis of paranoid condition. Part VI. Psychogenesis and Psychotherapy of the Manic Depressive Psychosis: cases of depressed and mixed types.

These many case histories are recorded under such headings as family history, personal history, relationship to father and mother, early and later sexual history, relationship to homosexuality, onset and symptomatology, sadism and masochism, and mechanisms in conflict. One case includes 24 dreams with interpretations. The case of a young woman showing sadism and masochism covers nearly 42 pages. Stealing, drinking and narcotic indulgence were but minor matters. Her sexual performances were so varied and frequent, that the degenerate women of history stand revealed as lacking in appeal. Were Freud, Adler, Jung, Steckel, Ferenczi and others in nearer accord, psychoanalysis would speak more convincingly. The index is ample, a glossary shows the ever-enlarging nomenclature, but additional methods should appear in a Mental Therapy. N. Y.

SOCIALIZED MEDICINE IN THE SOVIET UNION. By HENRY E. SIGERIST, M.D., William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Pp. 378; illustrated. New York: W. W. Norton & Co., Inc., 1937. Price, $3.50.

SOCIALIZED medicine can exist in its true form only as an integral part of a completely socialized state, and the author presents the characteristics of medical organization that evolve from the doctrines of socialism, which are the foundations of the present Russian government. After learning the Russian language, the author spent the summers of 1935 and 1936 in Russia, and not only made many observations of the medical organization, but also collected much documentary material regarding the official plans for medical service in the Soviet Union. He has long been interested in the theories of socialism, and presents a picture of Russian medicine as one phase of a rapidly moving and vast human drama, in which socialism is on trial. He has aimed to describe the advantages of socialized medicine, as compared with the medicine of Western Europe and of America, with which he is widely familiar, and has not attempted a critical analysis of its weaknesses or of the obstacles to its practical application.

The author points out that the Soviet Union is the first country to socialize medicine, and the first to consider the protection of the health of all the people a public function of the state. Although he recognizes inadequacies and shortcomings, both as to facilities and administration, his study leads him to conclude that medicine in the Soviet Union today is the beginning of a new period, the period of preventive medicine, as contrasted with the period of curative medicine of the past five thousands years.

Medicine in Russia today is an integral part of a great experiment in human relations, which will be observed and studied with such interest for years to come. The author has presented a significant phase of this fundamental experiment in a book which throws light on the Russia of today, illuminating a broader field than that related strictly to health and to disease G. R.

THE ENDOCRINES IN THEORY AND PRACTICE. Articles Republished from the British Medical Journal. Pp. 278. Philadelphia: P. Blakiston's Son & Co., 1937. Price, $3.50.

THIS is a publication in book form of a series of articles which were written on request of the *British Medical Journal* in 1936 and 1937 by Langdon-Brown, Dodds, Harington, Biggart, McCarrison, Fraser, Robson, and many others. The form of presentation is very simple, and obviously intended for those in general practice who do not have the time for following at first hand the complicated ramifications of the literature on hormones. Occasionally personal viewpoints, not generally accepted, obtrude; but on the whole anyone needing a book of this type will find it more accurate than most simplifications tend to be. I. Z.

Surgery of the Sympathetic Nervous System. By George E. Gask, C.M.G., D.S.O., F.R.C.S. (Eng.), Emeritus Professor of Surgery, University of London; Consulting Surgeon, St. Bartholomew's Hospital; and J. Paterson Ross, M.S. (Lond.), F.R.C.S. (Eng.), Professor of Surgery, University of London; Surgeon and Director of the Surgical Unit, St. Bartholomew's Hospital. Pp. 191; 49 illustrations (4 in color). Second edition. Baltimore: William Wood & Co., 1937. Price, $4.50.

In this book, the thoraco-lumbar portion of the autonomic nervous system is considered without the cranial and sacral portions. No morbid anatomy is given since none is known, except when there are tumors of the ganglia. Previously, these authors regarded the late results of sympathectomy as depending upon "the powers of the sympathetic to regenerate, and of the organs to function independently of their nerve supply;" but it is now believed the later results depend mostly upon the nature of the disease. Among new features included are the clinical gradings and prognosis in Raynaud's disease, recognition of localized structural disease of the main arteries, afferent pathways in the sympathetic system, and sympathectomy for dysphagia. The results obtained are not always clearly stated, but they are concerned with disorders of the circulation: operations for sympathetic denervation of the extremities and effects of cervico-thoracic ganglionectomy; disorders of the visceral motor mechanism in the alimentary canal and urinary tract; in dysmenorrhea, vesical and rectal pain, angina pectoris, and in causalgia. It is suggested that individuals who show "temperament" may have imperfect cerebral cortical control of centers in the hypothalamus. There is a selected bibliography at the end of each chapter and a fair index. The appearance of a second edition in less than 4 years speaks of increasing interest in this constructive work.

N. Y.

Maternal Deaths – The Ways of Prevention. By Iago Galdston, M.D., Secretary, Medical Information Bureau of the New York Academy of Medicine. Pp. 115. New York: The Commonwealth Fund, 1937. Price, paper, 50c.; cloth, 75c.

This clear, concise and factually accurate discussion of the several aspects of maternal mortality is intended for laymen, physicians and allied medical services. The author has drawn upon several of the recent reports on the subject, notably the study in New York City by a committee of the Academy of Medicine, for the basic material. The various factors concerned in maternal deaths, antepartum care, attendant, place and manner of delivery, influence of Cesarean section and of anesthesia and analgesia, abortion are assayed in terms of responsible influence. The answer, what can be done? as he so clearly shows concerns the entire community, public and profession, hospital and schools, health departments and community organizations. The part each element should play is honestly and straightforwardly given us.

P. W.

Short Years. The Life and Letters of John Bruce MacCallum, M.D., 1876–1906. By Archibald Malloch. Pp. 343; illustrated. Chicago: Normandie House, 1938. Price, $3.50.

J. B. MacCallum's scientific achievements as a student–well-known to medical students of the Reviewer's day, who were only a few years his junior—have inevitably faded into the back-ground as time has marched on. This sympathetic account by a personal friend not only perpetuates his example of notable achievement early in scientific life; but also gives an inspiring account of a sensitive soul's brave and successful fight to the end against chronic ill health. MacCallum's later important California studies on purgatives led Jacques Loeb to recognize him as a remarkably skillful investigator of the type "whom we may designate as discoverers. His results were obtained quickly, were made secure beyond doubt, and were put into such shape that they could easily be demonstrated by him." "St. John," as Osler nicknamed him, was to Osler "one of the most brilliant young men whom it has been my lot to teach." A prolific letter-writer and diarist, a story writer and poet of merit, he was undoubtedly one of the greatest of that notable group that Canada has lent to medicine in this country. He is then a conspicuous example of Plautus' truth, "Quem di diligunt, adolescens moritur." This account of his life and letters will be read with interest by many beside his personal friends. E. K.

Physiological Chemistry of the Bile. By Harry Sobotka, Chemist to the Mount Sinai Hospital, New York. Pp. 202; 4 illustrations. Baltimore: The Williams & Wilkins Company, 1937. Price, $3.00.

The present volume is a very admirable attempt to collect and correlate physiological, pharmacological and pathological data upon bile. Both experimental and clinical material are collected under the various subjects chosen for discussion. Two short chapters deal with the origin and quantity of hepatic secretion. Approximately 50 pages are devoted to the composition of the bile; one-third of this space being upon the bile acids and their interrelations, while the remainder is devoted to the other normal constituents and the chemical properties inherent in such a complex secretory product. The chemistry and physiology of the bile pigments were excluded, for its inclusion would require extensive reference to blood pigments and pyerol chemistry. Non-physiological constituents of bile, and the processes of detoxification are discussed briefly. The influence of various chemical, physical and biological factors that can be considered either as choleretics or cholagogues are reviewed extensively. Evidence is summarized also upon the presence of bile acids outside of the biliary tract, *e. g.*, in feces, urine, normal and icteric blood, etc. The concluding chapter is upon the effects of bile acids upon chemical and biological reactions and processes, including their effects in digestion and resorption of fat, their action on enzymes, their effects upon blood cells and microörganisms, and the pharmacological effects on the various organs of higher animals. A bibliography of nearly 1200 references is appended.

Analytical methods for determining the various important bile constituents are not discussed in this volume, this being reserved for a companion volume on the "Chemistry of Sterids." I. R.

Pediatric Urology. In two volumes. By Meredith F. Campbell, M.S., M.D., F.A.C.S., Professor of Urology, New York University College of Medicine, and Associate Attending Urologist, Bellevue Hospital, etc. With a Section on Bright's Disease in Infancy and Childhood, by John D. Lyttle, A.B., M.D., Assistant Professor of Diseases of Children, College of Physicians and Surgeons, Columbia University, etc. Pp. 1116; over 1350 illustrations and 2 colored plates. New York: The Macmillan Company, 1937. Price, $15 the set.

These two volumes break new ground for a medical text, and one need not look for comparisons by which to weigh it, for such do not exist. "Pediatric urology is still in its diaper age," states the author, and he has made this effort "to indicate to practitioners in general, and to pediatrists and urologists in particular, the clinical aspects of urologic disease in infants and children." His background has been his work, now well known to his colleagues for many years, with over 1000 pediatric beds in 4 large New York hospitals, and also 4 Out-patient Departments. To this is added the tabulated studies of 12,080 postmortem examinations on infants and children. From this experience of over 10 years the statement is made that, "about half of all children suffer some form of urologic disturbance before they reach puberty. Although a large portion of these conditions are of a minor nature, and many pass unrecognized, the field of Pediatric Urology still remains of unexpected enormity."

Volume I starts with methods of examination and diagnosis, and it is rapidly developed that no method of investigation now used in the adult is denied the infant or child. There follow chapters on the many-sided problem of obstructive uropathies; the wide field of anatomy and the anomalies; and then the long-mooted topic of urinary infections. This last chapter is a monograph that stands alone, and would that every pediatrician and every urologist could read it. (Surely the world would be better!)

Volume II starts with a chapter on Bright's disease by the author's collaborator, Dr. Lyttle; followed by chapters devoted to genital disease; urogenital injuries; calculus disease; tumors; neuromuscular disease; enuresis; and urosurgery.

The text is beautifully and excellently illustrated, and where necessary, both tabulations and case reports are inserted. The bibliography is complete, as likewise the index. One could expatiate in glowing terms on this welcome addition to urology, and silently pray that the pediatric world will mark, heed and inwardly digest. A. R.

DIE WERKE DES HIPPOKRATES. Part 16. Der Samen / Das Werden des Kindes / Das Herz / Die Geistesstörung / Die Tollwut / Die Nieswurzanwendung. (On Generation; On the Nature of the Infant; On the Heart; On Mental Disturbance; On Hydrophobia; On the Administration of Hellebore.) Pp. 95, Price, Rm. 7.50. Part 17. Die Leiden / Die Krankheiten, 1. Buch. (Of Affections; Of Diseases, Book 1.) Pp. 102. Price, Rm. 8. Part 16. Ubersetzt von DR. MED. RICHARD KAPFERER, Facharzt für Physikalisch-diätetische Behandlung. Part 17. Herausgegeben von DR. MED. RICHARD KAPFERER, Bad Wörtshofen und München, unter Mitwirtung von Prof. DR. GEORG STIDER, Würzburg, u. a. (To be published in 25 parts costing ca. Rm. 100, card binding.)

PART 16. "Generation" and "The Nature of the Child" are the largest of the treatises in this booklet. They probably, according to Kapferer, were originally combined as the fourth book of "Diseases." The work is chiefly concerned with the normal and abnormal processes that develop the seed into the embryo and the infant. Hippocrates' comparison of the effect of natural forces on fauna and flora support his important opening generalization that the laws of Nature are omnipotent. The impotence of eunuchs is of course recognized, and the explanation of various congenital anomalies is attempted. One can read into the text beliefs on causality and heredity that are surprisingly compatible with modern views.

The 10 short pages on "The Heart" include remarkable descriptions of that organ, its chambers, valves and appendages. Though the author appreciated the central importance of the heart and recognized the vessels coming to and leading from the two ventricles, a true circulation is far from being visualized. The left ventricle, the seat of the soul, is regarded as the place where the nourishing air coming from the lungs is cooked with blood elements to make the arterial blood. That the left ventricle was not nourished by visible blood was proven to the author by the fact that it was found empty in slaughtered animals.

The sections on Mental Disturbance, Hydrophobia and Administration of Hellebore, are taken by Kapferer from the newly discovered version of the "Letters of Hippocrates" in the Urbinas 68 s XIV Manuscript. They are regarded by the editor as truly Hippocratic both because of their lines of thought and diction and because they fill in a section that, though lacking in the accepted Corpus Hippocraticum, is referred to in the work on "The Sacred Disease." There mental disease is divided into two groups caused by retention and mucus in the brain and by influx of bile into the brain, respectively. Only the former is treated, while the latter forms the topic of the 19th letter, but in this manuscript in ten-fold longer form. The Administration of Hellebore is from the 21st letter. These important additions to the Corpus appears here in a modern language for the first time.

Part 17. "The Affections," usually regarded as of Cnidian origin, was said by Galen to have been written by Polybos, the son-in-law of Hippocrates. Apparently intended for the medical apprentice (not the laity), it sketches the general causes of disease before taking up treatment. Derangements of bile and mucus are most important, whether from macrocosmic (heat, cold, etc.) or microcosmic (diet, effort, wounds, sexual activity, impressions on special senses) causes. The seven fluxes from the head (to the ear, nose, eyes, thorax, abdomen, skin and joints and the vertebral column) produce various diseases in each region, to be treated by various means, physical, dietary, surgical and medical. Enemas, emetics and purgatives are favorites used in many different conditions.

"The Disease" also is said by Galen and Diocorides to come from Polybos, but by others to be Cnidian. It also treats of the macrocosmic and microcosmic causes of disease. Discussion of the course of wound healing and of diseases leads to outlines of correct diagnosis. The pathogenesis of empyema, "erysipelas" and ulcers (tuberculosis) of the lung, of fever, chills, sweats, is explained on the basis of the doctrine of the four humors.

E. K.

An Analysis of the De Generatione Animalium of William Harvey.

By Arthur William Meyer, Professor of Anatomy, Stanford University. Pp. 167; illustrated. Stanford University: Stanford University Press, 1936. Price, $3.00.

Though Harvey will undoubtedly always be chiefly remembered for his immortal discovery of the circulation of the blood, admirers have not been lacking to extol his later work on the Development of Animals. It is indeed surprising, then, that the author of this Analysis should have found that, in the 144 Harvaeian Orations which have been given in London, this book should never have received adequate attention and indeed never even been mentioned until 1872. He has only been able to find three recent works that have given more than scant attention to *De Generatione*, so that the present volume is the first considerable analysis of a work that was much longer and more complex than its more famous predecessor. In the present work one passes from a consideration of the times and of previous and contemporary embryologists to an analysis of the treatise itself, Harvey's version of epigenesis, his aphorism *ex ovo omnia* (so frequently distorted into *omne vivum ex ovo*), his views on fertilization and so on. One is forced to agree with the author that the same method that led Harvey to the successful solution of the problem of the circulation failed to discover the mysteries of generation or even materially to promote the search. *De Motu* "was a brief, clear, convincing, and decisive demonstration, revolutionary in both nature and effect while the *De Generatione* was long, obscure, speculative, and inconclusive in both nature and effect." This is not permitted to hide the merits of Harvey's work: his use of the scientific method whenever possible, his numerous keen observations and shrewd reasoning, his many-sided and long-sustained attempt to prove *ex ovo omnia*, and the superiority of his book to those on the subject by his contemporaries. It is also true and worth emphasizing that Harvey's eminence is so well established by his immortal discovery that it need not be supported by exaggerated claims for his less successful effort. E. K.

A DISSERTATION ON ACUTE PERICARDITIS. By OLIVER W. HOLMES. Introduction by JAMES F. BALLARD, Director, Boston Medical Library. Pp. 39. Boston: The Welch Bibliophilic Society, 1937. Price, $7.50.

THOUGH Holmes did not study in the Harvard Medical School, he was given his M.D. degree by Harvard in 1836, after having taken courses in a private medical school, "walked the hospitals" of Paris for two years and practised a year in Boston. For his dissertation, which was then a prerequisite for the degree, he wrote on Acute Pericarditis; but as Ballard explains in the Introduction, the manuscript has remained unnoticed in the Boston Medical Library, not having been mentioned by either his biographer, Morse, or his bibliographer, Ives. It now appears in print for the first time. Though, like most dissertations, it contributed little more than the current knowledge of the subject, this in itself is of interest on account of the great productive activity of the French School at that time. More interesting is the characteristic vein of humor that frequently crops up to the surface and the fact that, for reasons not given, the thesis was prepared "entirely in the span of little more than 3 days." E. K.

A TEXT-BOOK OF OPHTHALMIC OPERATIONS. By HAROLD GRIMSDALE, M.B., F.R.C.S., Consulting Ophthalmic Surgeon to St. George's Hospital; Consulting Surgeon to the Royal Westminster Ophthalmic Hospital, and ELMORE BREWERTON, F.R.C.S., Consulting Ophthalmic Surgeon to the Metropolitan Hospital; Consulting Surgeon to the Royal Westminster Ophthalmic Hospital. Pp. 322; 105 illustrations. Third edition. Baltimore: William Wood & Co., 1937. Price, $6.00.

THE third edition of this text contains the newer operations for detachment of the retina. The illustrations as in the first edition are not good. The book can only be recommended as a résumé of the methods employed by English ophthalmic surgeons. F. A.

CHEMISTRY OF THE BRAIN. By IRVINE H. PAGE, A.B. (CHEM.), M.D., Hospital of The Rockefeller Institute for Medical Research, New York. Pp. 444. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

THE growth of our knowledge of sterols and their very wide biological importance has resulted, as is to be expected, in the publication of a number of excellent monographs upon the subject. The present volume by Dr. Irvine H. Page is not merely a further treatment of sterol chemistry. If Dr. Page were writing in the language of J. L. W. Thudichum, a history of whose pioneer efforts in brain chemistry prefaces the work, the book might bear the following descriptive title: "The chemistry, chemical pathology and physiology of the brain and nerve tissue, giving the clinical applications of the same, as well as the interrelationships of the organ of thought to the body as a whole."

Such a title the Reviewer believes would cover more aptly the generous extent of Dr. Page's work. Not only is the chemistry of the sterolic brain substances treated, but adequate space is devoted to what is known of carbohydrate metabolism, water balance, nitrogen metabolism, vitamin and enzyme activity, and oxidation-reduction processes as they apply to brain and nerve tissues.

The treatment is most readable throughout, and, in a number of instances provocative. For example, in the last chapter, "The Brain and Thought," Dr. Page discusses, among other things, the ambiguity in the word "ought," used by scientists on the one hand or by religionists on the other. It is not clear to the Reviewer whether Dr. Page has settled the question "ought a man murder his wife?" They are, of course, countless problems which are raised in work of this sort, and which future research no doubt will solve.

The "Chemistry of the Brain" is recommended highly to all workers in the biological sciences, and should prove of especial interest to those engaged in research and treatment of nervous and mental disease.

D. D.

DIE DIFFUSIONSANALYSE AM BLUTPLASMAGEL. Ein Neuer Weg der Blutforschung. By RUDOLF BUCHER. Pp. 123; 70 illustrations (30 in color). Basel: Benno Schwabe & Co., 1937. Price, Fr. 30.

LIESEGANG rings of silver bichromate were produced in citrate plasma which, after addition of potassium bichromate, had been transformed into a gel by the addition of Ca and then covered by silver nitrate solution. The procedure described in detail allows a fairly satisfactory reproducibility of the ring formation in regard to time of appearance as well as distances between the rings. Comparing a great number of plasma samples, characteristic differences in the arising structures were observed depending upon the origin of the plasma and upon physiological conditions. Age, sex, species are shown to be of importance. Arterial plasma is different from venous plasma. After strong bleeding the plasma gives no rings at all. Anesthesia with ether or chloroform, shock experimentally produced, *e. g.*, by mechanical stimulation of the abdominal sympathetic, slow down the appearance of the ring structure. The results are illustrated by excellent pictures, 30 of them in colors.

R. H.

PRACTICAL PHYSIOLOGICAL CHEMISTRY. By PHILIP B. HAWK, M.S., PH.D., President of the Food Research Laboratories, Inc., New York City, and OLAF BERGEIM, M.S., PH.D., Associate Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. In Collaboration with BERNARD L. OSER, PH.D., Director of the Food Research Laboratories, Inc., New York City, and ARTHUR G. COLE, PH.D., Assistant Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. Pp. 968; 281 illustrations. Eleventh edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $8.00.

THE eleventh edition of this well known textbook contains much new material. Many chapters have been entirely rewritten, the list marking the fields of biochemistry in which most notable advances have been made—the vitamins, enzymes, endocrines, digestion, bile, putrefaction and detoxication, blood and tissue analysis and the teeth. As ever it is unexcelled as a practical manual.

E. W.

MAN AGAINST HIMSELF. By KARL A. MENNIGER. Pp. 485. New York: Harcourt, Brace and Company, 1938. Price, $3.75.

UNDER appropriate captions, detailed study is made of such varied subjects as asceticism and martyrdom, neurotic invalidism, alcoholic addiction, anti-social behavior, psychoses, self-mutilations, malingering, impotency and frigidity. Inspired by Freud's hypothesis of man's propensity for self-destruction, the author endeavors to show that by a sort of psychosynthesis, these variant, instinctively destructive forms of suicide, may lead one logically to a process of self-preservation.

Asceticism and martyrdom are accorded most space. Among historic martyrs is Simeon Stylites who was idolized by his parents, but whose brutal repulsion contributed to their death. A quote from Lecky's description of the saint's monastery life reads: "A horrible stench, intolerable to the bystanders, exhaled from his body, and worms dropped from him whenever he moved and they filled his bed . . ." After having built three pillars, he mounted the last, which was 60 feet high, and there lived for 30 years. During an entire year, "St. Simeon stood upon one leg, the other being covered with hideous ulcers, while his biographer was compelled to stand by his side, to pick up the worms that fell from his body, and to replace them in the sores, the saint saying to the worm, 'Eat what God has given you.'" A less gloomy church version of the saint is available.

As in "The Human Mind," the author employes a non-technical, popular, dramatic style, which has given us a book that is interesting and stimulating to the imagination. However, an implication by Havelock Ellis is recalled: " . . . the psychoanalyst is a kind of spider who spins his pathological web-complex so vividly and so elaborately . . . in the hope that somewhere . . . the fly must be entangled." N. Y.

CLINICAL ALLERGY. Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. Manifestations, Diagnosis and Treatment. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco; Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland, Calif., etc. Pp. 812. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

SIX years ago, Dr. Rowe published his excellent book on food allergy. The present volume is obviously the result of expanding that volume to cover the whole field of allergy. The author has certainly succeeded in covering the field, but the major emphasis, one may say overemphasis, remains on food allergy. Thus after chapters on the nature, mechanism, origin and characteristics of allergy and the diagnosis of allergy, come chapters on the "Treatment of Food Allergy by Elimination Diets and General Measures," and on "Gastrointestinal Allergy," before asthma or other respiratory tract manifestations of allergy are considered. However, one may well pardon the overenthusiasm for food allergy on the part of a man who has made so many important contributions to our knowledge of the subject. Of particular value is the enormous amount of clinical case material which the author has gathered, both from his own large experience and the literature, to illustrate the many phases of clinical allergy. There are numerous and well selected references to the huge literature in this field, but theoretical matters are at times vaguely stated or not interpreted with strict accuracy. There are, on the whole, surprisingly few mistakes even for a first edition (*e. g.*, pyrethrum *leaves* instead of *flowers* used as insecticides; attributing to Baum priority in the exclusively allergic etiology of nasal mucous polyps). No one interested in the field of allergy can afford to be without this important work and all internists will find it a very helpful book of reference.

R. K.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago. Pp. 642; 8 illustrations. Third edition, revised. Philadelphia: J. B. Lippincott Company, 1937. Price, $5.00.

THAT a third edition has been called for since its appearance in 1934 testifies to the popularity of this very practical presentation of the subject. Discussions of the clinical aspects of current knowledge of the vitamins, the use of protamin-zinc insulin and an enlarged section on diet in the treatment of obesity are the new material in the volume. R. K.

NEW BOOKS.

The Biology of Pneumococcus. The Bacteriological, Biochemical, and Immunological Characters and Activities of Diplococcus Pneumoniæ. By BENJAMIN WHITE, PH.D., with the collaboration of ELLIOTT STIRLING ROBINSON, M.D., PH.D., and LAVERNE ALMON BARNES, PH.D. Pp. 799; illustrated. New York: The Commonwealth Fund, 1938. Price, $4.50.

Eighth International Congress of Military Medicine and Pharmacy and Meetings of the Permanent Committee, Brussels, Belgium, June 27–July 3, 1935. Report of CAPTAIN WILLIAM SEAMAN BAINBRIDGE, M.C.-F., U.S.N.R., Ret., Member of the Permanent Committee for the Delegation of the United States of America. Pp. 114; illustrated.

The Time Has Come. . . . (The Harveian Oration Delivered Before the Royal College of Physicians of London on St. Luke's Day, 1937.) By SIR ARTHUR HURST, M.A., D.M. (OXON.), Senior Physician to Guy's Hospital; Fellow of the College. Pp. 42. London: Headley Brothers, n.d. Price, 5/–.

The two hundred and eighteenth Harvey Oration, though it perforce neglects some of the instructions of the immortal donor, complies at least with the exhortation to search and study out the secrets of Nature by way of experiment. The orator has sketched the recent advances in knowledge of disordered gastric physiology in relation to anemia—Beaumont, Spallanzani, Fenwick, Faber, Castle, Hurst and Bell—and to the pathogenesis of gastric carcinoma.

The Treatment of Clinical and Laboratory Data. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By DONALD MAINLAND, M.B., CH.B., D.Sc. (EDIN.), Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia. Pp. 340; 23 illustrations. London: Oliver and Boyd, 1938. Price, 15/–.

The Patient and the Weather. Vol. IV, Part 3, Organic Disease. Surgical Problems. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Pp. 651 (lithoprinted); 482 illustrations. Ann Arbor: Edwards Brothers, Inc., 1938. Price, $10.00.

Claude Bernard, Physiologist. By J. M. D. OLMSTED, Professor of Physiology, University of California. Pp. 272; illustrated. New York: Harper & Brothers Publishers, 1938. Price, $4.00.

Handbook on Social Hygiene. Edited by W. BAYARD LONG, M.D., Attending Dermatologist and Director of Dermatology and Syphilis Clinics in St. Luke's Hospital, New York, etc., and JACOB A. GOLDBERG, M.A., PH.D., F.A.P.H.A., Secretary, Social Hygiene Committee, New York Tuberculosis and Health Association, and Social Hygiene Council of Greater New York. With a Foreword by EDWARD L. KEYES, M.D., Professor Emeritus of Clinical Surgery (Urology) in Cornell University Medical College, New York. Pp. 442; 62 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.00.

Contributions to Medical Research. Anniversary Volume. Scientific Contributions in Honor of JOSEPH HERSEY PRATT on his Sixty-fifth Birthday. (Reprinted from articles appearing in Annals of Internal Medicine.) Pp. 983; illustrated. Printed by Lancaster Press, Inc., Lancaster, Pa., 1937. Price, $7.00.

Das Rheumabuch des Doctor Ballonius. Nach der Rheumaschrift des Lateinischen Textes. Gulielmi Ballonii, Liber de Rheumatismo et Pleuritide Dorsali, Paris, 1642. Deutsch Herausgegeben von Dr. Walter Ruhmann, Specialarzt für Innere Krankheiten in Berlin. Pp. 66; 1 illustration. Mittenwald: Arthur Nemayer, 1938. Price, Rm. 3.

Zeitschrift fur Rheumaforschung. Band 1, Heft 1, Januar, 1938. Herausgegeben von Dr. P. Köhler, Geh. San.-Rat, Leiter d. Staatl. Rheumaheilanstalt u. d. Sanatoriums Bad Elster, Prof. Dr. Rud. Jürgens, Stellv. Dir. d. Univ.-Klinik für natürl. Heil- und Lebensweisen, Berlin. Für den Referatenteil: Dr. H. Kaether, Univ.-Klinik für natürl. Heil- und Lebensweisen, Berlin. Unter Mitwirkung von Th. Fahr, Hamburg; F. Frik, Berlin; G. Hohmann, Frankfurt a. M.; P. Rostock, Berlin; R. Schoen, Leipzig; A. Slauck, Aachen; H. Vogt, Breslau. Pp. 40; 13 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Quarterly, Rm. 7.50; Yearly, Rm. 30.

Journal of Neurophysiology. (Issued Bi-monthly). *Vol. 1, No. 1, January, 1938.* Editorial Board: J. G. Dusser de Barenne (Yale), J. F. Fulton (Yale), R. W. Gerard (Chicago). Advisory Board: E. R. Adrian (Cambridge); P. Bailey (Chicago); P. Bard (Baltimore); G. H. Bishop (St. Louis); F. Bremer (Brussels); D. Bronk (Philadelphia); E. von Brücke (Innsbruck); S. Cobb (Boston); H. Davis (Boston); U. Ebbecke (Bonn); J. C. Eccles (Sydney); J. Erlanger (St. Louis); W. O. Fenn (Rochester); A. Forbes (Boston); H. S. Gasser (New York); R. Granit (Helsingfors); W. R. Hess (Zurich); Marion Hines (Baltimore); Davenport Hooker (Pittsburgh); R. Lorente de Nó (New York); W. Penfield (Montreal); H. Piéron (Paris); S. W. Ranson (Chicago); G. van Rijnberk (Amsterdam); C. S. Sherrington (Ipswich). Pp. 85; illustrated. Springfield, Ill.: Charles C Thomas, 1938. Price, $6.00 per volume.

The Thousand Forms of Disease. By R. P. Byers, M.A. Pp. 29. Boston: Super-university Publications, 1938. Price, $1.50.

A Biological Approach to the Problem of Abnormal Behavior. By Milton Harrington, M.D., Psychiatrist, Institution for Male Defective Delinquents, Napanoch, N. Y.; Formerly Consultant in Mental Hygiene, Dartmouth College. Pp. 459; illustrated. Lancaster: The Science Press Printing Company for the Author, 1938.

Introduction to Ophthalmology. By Peter C. Kronfeld, M.D., Professor of Ophthalmology, The Peiping Union Medical College. Pp. 331; 32 text illustrations and 5 plates. Springfield, Ill.: Charles C Thomas, 1938. Price, $3.50.

Clinical Roentgen Therapy. Edited by Ernst A. Pohle, M.D., Ph.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wisconsin. Foreword by George W. Holmes, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology in Harvard Medical School, Boston. Pp. 819; 199 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Workbook in Elementary Diagnosis for Teaching Clinical History Recording and Physical Diagnosis. By Logan Clendening, Professor of Clinical Medicine, University of Kansas. Pp. 167; illustrated. St. Louis: The C. V. Mosby Company, 1938. Price, $1.50.

Practical Procedures. (The Practitioner Handbooks.) Edited by Sir Humphry Rolleston, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and Alan A. Moncrieff, M.D., F.R.C.P. With a Preface by Sir David Wilkie, O.B.E., M.D., M.Ch., F.R.C.S., F.A.C.S., F.R.S.E. Pp. 293; 66 illustrations. London: Eyre and Spottiswoode (Publishers) Ltd., 1938. Price, 10s. 6d.

On Thought in Medicine (*Das Denken in der Medizin*). By HERMANN VON HELMHOLTZ. An Address delivered August 2, 1877, on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons. Introduction by ARNO B. LUCKHARDT. (Reprinted from Bulletin of the Institute of the History of Medicine, Vol. 6, No. 2, February, 1938.) Pp. 27; 2 illustrations. Baltimore: The Johns Hopkins Press, 1938. Price, 75c.

Diabetes Insipidus and the Neuro-hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System. By CHARLES FISHER, PH.D., W. R. INGRAM, PH.D., and S. W. RANSON, PH.D., M.D., Institute of Neurology, Northwestern University Medical School. Pp. 212 (lithoprinted); 71 illustrations and 26 tables. Ann Arbor: Edwards Brothers, Inc., 1938. Price, $5.00.

The Brain and Its Environment. By JOSEPH BARCROFT, Professor of Physiology, Cambridge University. Pp. 117; 30 illustrations. New Haven: Yale University Press, 1938. Price, $2.00.

On a New Gland in Man and Several Mammals (*Glandulæ Parathyreoideæ*). By IVAR SANDSTRÖM [Upsala Läkareförenings Förhandlingar, 1879–80, 15, 441–471.] Translated by CARL M. SEIPEL, Dr. Med. Dent. Edited by CHARLOTTE H. PETERS and J. F. FULTON. With biographical notes by Professor J. AUGUST HAMMAR. Pp. 44; 1 illustration and 3 plates. Baltimore: The Johns Hopkins Press, 1938. Price, $1.00.

NEW EDITIONS.

X-rays and Radium in the Treatment of Diseases of the Skin. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University; Consulting Dermatologist, St. Luke's Hospital, etc. Pp. 830; 308 illustrations, 31 charts and 2 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to St. Bartholomew's Hospital, etc., and LAWRENCE P. GARROD, M.A., M.D., B.CH. (CAMB.), F.R.C.P. (LOND.), Professor of Bacteriology in the University of London; Bacteriologist to St. Bartholomew's Hospital, etc. Pp. 420; 65 illustrations. Third Edition. Philadelphia: P. Blakiston's Son & Co. Inc., 1938. Price, $5.00.

Pneumonia and Serum Therapy. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health, 1931–1935. Pp. 148; 10 figures and 10 tables. Revised edition of Lobar Pneumonia and Serum Therapy. New York: The Commonwealth Fund, 1938. Price, $1.00.

Medical Dictionary. II. Part. German-English. By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. Pp. 238. Seventh Edition. Wien: Franz Deuticke, 1938. Price, M. 7.

This pocket sized dictionary should be useful to many English speaking readers of German medical works. It can hardly be expected to be as satisfactory as larger volumes.

Management of the Sick Infant and Child. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Dean, University of California Medical School, and Professor of Medicine, etc., and WILLIAM E. CARTER, M.D., Director, University of California Hospital Out Patient Department, etc. Pp. 874; 94 illustrations. Fifth Revised Edition. St. Louis: The C. V. Mosby Company, 1938. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE
THERAPEUTICS

UNDER THE CHARGE OF
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THE USE OF SULPHANILAMIDE IN THE TREATMENT OF VARIOUS INFECTIONS.

WITHIN the past 2 years there has come into prominence a large number of reports concerning the experimental and clinical use of sulphanilamide and related chemical compounds in the treatment of various infections. While these chemicals have been used in a wide variety of infections, those resulting from hemolytic streptococci, meningococci, gonococci, and urinary tract infections have received most attention. It is the purpose of this short review to summarize a few of the more important results that have been obtained in these infections, and to emphasize the more important toxic manifestations of these compounds in man.

Terminology. Inasmuch as a number of compounds have been used in the treatment of various infections, it is well to summarize the nomenclature. The results recorded in the literature following the use of these various drugs have varied somewhat so that it is important to designate the proper name to the drug that is employed in each instance. Table 1 summarizes a few of the various drugs that have been used most widely. Of these, sulphanilamide and prontosil soluble have had the widest use in this country.

TABLE 1.—NOMENCLATURE.

1. Sulphanilamide—also known as
    - Para amino benzene sulphonamide
    - Prontosil album
    - Prontylin
    - *Stramid*
    - Streptocide
2. Prontosil—also known as
    - Prontosil red
    - Prontosil flavum
    - Sulphamido-chrysoidine
3. Prontosil Soluble

Pharmacology of Sulphanilamide. From the studies of Marshall, Emerson, and Cutting[14] it is known that the drug is absorbed from the gastro-intestinal tract with remarkable rapidity. Maximum concentrations in the blood are reached within 4 hours after its ingestion. It diffuses through all of the tissues, and resembles urea in its approximately even distribution throughout the body. Marshall and his associates have been able to show that skeletal muscles, heart muscle, liver, lung, and spleen contain the same concentration as blood. Skin contains slightly less, brain contains about two-thirds the concentration of blood, and bone and fat contain the drug in much lower concentration than blood. The drug is excreted in the urine and *nearly 100%* of the amount ingested can be recovered. Part of the drug becomes acetylated during its passage through the body but most of it is free and readily detected. Marshall has found that sulphanilamide is excreted entirely by glomerular filtration and that 70 to 80% of it is reabsorbed by the tubules. When there is impaired renal function sulphanilamide is excreted more slowly. For this reason it is necessary to give the drug to patients with renal insufficiency in smaller amounts and for a shorter duration of time. Since it is absorbed from the gastro-intestinal tract almost as rapidly as from the subcutaneous tissues, it is not necessary to give the drug subcutaneously in any patient unless he has excessive vomiting. The drug diffuses into the cerebrospinal fluid in about 80% of the concentration in the blood. It is not necessary, therefore, to give this drug intrathecally in cases of meningitis.

Treatment of Hemolytic Streptococcal Infection. *Puerperal Fever.* Extensive studies on the effect of sulphanilamide, prontosil soluble, and prontosil have been carried out in cases of puerperal fever by Colebrook and Kenny[5] and Colebrook and Purdie.[6] Keefer[11] has reported results in a small group of cases. Impressive results have been obtained with prontosil soluble, prontosil, and sulphanilamide. In Colebrook and Purdie's recent paper the comment is made that their results with sulphanilamide seem to be less effective than those obtained with prontosil soluble and prontosil. However, the average stay in hospital was reduced from 31.3 days before the use of the drug to 19.7 days following its use. Moreover, they have been able to reduce their average fatality rate from 22.8% in cases before the use of prontosil soluble and sulphanilamide to 5.5% in cases following its use. In a footnote, Colebrook and Purdie state that the death rate in all of their cases of infection by hemolytic streptococci treated with these drugs since August, 1936, has been 7%.

It is now recognized that the average fatality rate for all cases of puerperal sepsis due to hemolytic streptococci is between 15 and 25%. It is lowest in those cases with only a localized infection of the endometrium, and highest in those with bacteremia, peritonitis, or thrombophlebitis of the pelvic veins with metastases (50 to 70%). It might be anticipated, then, that the most striking results from the use of sulphanilamide would be obtained in those cases in which the death rate is lowest, and this turns out to be the case. In the bacteremic cases reported by Colebrook and associates, the fatality rate was 71% in the untreated cases over a 4-year period, and during the period in which patients were treated with prontosil soluble or sulphanilamide the fatality rate was 40%. In their last paper there were 15 bacteremic cases with 8 deaths. In some there was a mixed infection. In the cases limited to the uterus, vagina, and perineum there were no deaths.

From the studies so far reported it would appear, then, that in puerperal fever due to hemolytic streptococci the use of sulphanilamide, prontosil, and prontosil soluble reduces the fatality rate, especially in infections limited to the uterus, vagina, and perineum, and even in cases of bacteremia and peritonitis. The duration of the infection seems to be shortened, the hospital stay reduced, and the spread of the infection prevented.

Erysipelas. The fatality rate in erysipelas is highest under the age of 6 months and after the age of 50 years, especially in patients with bacteremia and debilitating diseases. From the reports of a few cases it would appear that both prontosil soluble and sulphanilamide are distinctly helpful in the treatment of this disease. There are cases in which recovery occurred in newly-born infants with bacteremia, and the fatality rate seems to be reduced in infants under 6 months of age. Furthermore, there is evidence that the lesion stops spreading and that the duration of fever is shortened in some cases following the exhibition of the drug. While it is difficult to decide just what effect these drugs have in individual cases, since the natural history of erysipelas varies so widely from case to case, evidence in accumulating that is highly suggestive of its beneficial effects.

Hemolytic Streptococcal Bacteremia. When hemolytic streptococcal infection is accompanied by bacteremia, the prognosis is extremely grave. In general, the fatality rate is in the neighborhood of 70%, although it varies with the site of the focus, the age of the patient, and the treatment employed. I have been able to collect 50 cases of bacteremia from the literature, including 12 cases of my own, in which bacteremia was observed in a patient treated with either prontosil soluble or sulphanilamide. The fatality rate in these cases was 32%, a figure that is distinctly lower than any untreated group. These observations are to my mind among the most convincing that these drugs are of distinct value in hemolytic streptococcal infection.

Hemolytic Streptococcal Meningitis. Everyone is agreed that hemolytic streptococcal meningitis is the most serious of all hemolytic streptococcal infections. It has been established that the fatality rate in these cases is in the neighborhood of 98%. From 1901 to 1937 there were 110 recorded recoveries in the literature (Gray,[8] Trachsler[18]). Since 1937 with the introduction of prontosil soluble there are at least 40 cases reported that have recovered, and while it is too soon to say what the fatality rate will be in this disease, it is safe to assume that more than one-half of the cases can be treated with a satisfactory outcome. These results are indeed very outstanding and remarkable.

Tonsillitis and Scarlet Fever. So far there is little convincing evidence that the clinical course of scarlet fever or tonsillitis is affected by the use of sulphanilamide or prontosil soluble. Whether or not it will reduce the number of suppurative complications in this group of infections will have to be decided from additional studies.

In brief, then, there seems to be no doubt that sulphanilamide and related compounds have a profound effect on the course of hemolytic streptococcal infections. The most striking effects have been observed in puerperal sepsis, hemolytic streptococcal meningitis, and in cases of bacteremia. There are other infections in which it is difficult to decide, or in which the present data are insufficient to draw an accurate conclusion. These include tonsillitis, sore throat, and erysipelas.

Treatment of Meningococcal Infection. Following the observations of Proom,[16] Brown,[3] Branham and Rosenthal,[2] and others that sulphanilamide and related compounds are capable of protecting mice against fatal infection when the mucin technique of Miller is used, these drugs have been employed in the treatment of meningococcal meningitis. As related above, sulphanilamide diffuses into the cerebrospinal fluid with ease when it is taken by mouth, and it is present in about 80% of the concentration of the blood, so that it is not necessary to give it intraspinally. Schwentker[17] reported a 15% fatality rate in 52 patients treated for meningococcal meningitis. Place[15] of the South Department of the Boston City Hospital informs me that their fatality rate has been 25% in the cases treated with sulphanilamide alone. This is approximately one-half the fatality rate obtained in both clinics from which the reports came when antiserum was used. I have treated 2 patients with excellent results. While it would be premature to say that sulphanilamide was as effective in the treatment of meningococcal infection as specific antiserum, the evidence available at present indicates that it is an effective form of treatment and it has the advantage that one does not have to introduce foreign protein to the cerebrospinal system.

Treatment of Gonococcal Infection. Following the report of Colston and Dees[7] a great many patients have been treated with sulphanilamide for gonococcal infection, including urethritis, cervicitis, gonococcal ophthalmia, vulvovaginitis of children, pelvic peritonitis, and arthritis. The reports that have been written concerning the results are somewhat conflicting. There seems to be no doubt that in some series of cases at least, one-half of the instances of urethritis are completely relieved within 7 days of treatment. In others, the course is more chronic and, in some, it seems to be completely ineffective. It has been emphasized on a number of occasions that following the administration of the drug by mouth, the discharge from the urethra diminishes, the symptoms subside, but gonococci can still be obtained from urethral and prostatic exudates. These observations serve to emphasize the importance of careful examination of exudates for the presence of gonococci, even after the acute stage of the process has subsided.

It has been found, from a study of the blood of patients receiving sulphanilamide, that the bactericidal power for the gonococcus increases greatly, and that this property of the blood is maintained as long as the drug is continued in adequate dosage. Moreover, it has been possible in a few cases to sterilize infected synovial fluid within 2 days after the exhibition of the drug. From such studies it seems likely that sulphanilamide will be effective in preventing bacteremia, and that it will be an aid in clearing foci of infection. In spite of the reports in which failures have been recorded, there are good experimental and clinical reasons for believing that the use of this drug in the treatment of gonococcal infection will prove to be a most helpful therapeutic agent.

Treatment of Urinary Tract Infections. One of the characteristic features of sulphanilamide is its bacteriostatic effect on the growth of various bacteria. This property has been used in the treatment of urinary tract infections due to *B. coli, Hemophilus influenzæ, B. proteus,* and *Staphy. aureus.* Helmholz[10] also states that sulphanilamide is bactericidal and that it can be used in the acute stage of urinary tract infection. He maintains that it is active in an alkaline urine and can be used in the face of renal insufficiency. In his experience it has had favorable action in all of the infections except *Strep. fecalis.* Bliss and Long[1] have reported failures with the use of sulphanilamide in streptococcal infections due to Group D (Lancefield). Our experience with the drug indicates that the drug is bacteriostatic and frequently reduces the number of organisms without producing a complete sterilization of the urine. In some cases, however, the organisms disappear entirely during the administration of the drug and reappear once it is discontinued. In others, complete recovery follows and, in another group, no effect seems to be evident. That it is a drug of value in these infections, no one can deny, but it is entirely too early to say just what its field of greatest usefulness will be in the future.

Toxic Manifestations of Sulphanilamide. While sulphanilamide has a relatively low toxicity for animals it is known that certain individuals respond in a way that is exceedingly alarming and, indeed, dangerous. The various toxic manifestations are summarized in Table 2.

TABLE 2.—TOXIC MANIFESTATIONS.

Symptoms and signs.	Time of appearance.	Treatment.	Outcome.
Cyanosis	First or second 24 hours	None—unless there are symptoms of anorexia; then discontinue drug	Recovery is prompt.
Nausea Vomiting Giddiness Weakness	First 24 hours or longer	None—it is usually not severe enough to discontinue drug	
Anemia	3 to 7 days	Stop drug immediately Force fluids to 3000 cc. daily Blood transfusions	Recovery from blood transfusion.
Agranulocytosis	14th day or later	Stop drug Pentnucleotide Blood transfusion	Fatal in most cases.
Fever	7th to 9th day Usually continues 2 to 6 days Varies from 101° to 106°	Discontinue drug Force fluids	Complete recovery.
Skin rash	7th to 9th day Usually accompanied by fever	Discontinue drug Force fluids	Complete recovery.

Cyanosis. Cyanosis of the skin and mucous membranes following the administration of sulphanilamide is exceedingly common and, in fact, when adequate dosage is given it is almost always present. It has been attributed to the presence of sulphhemoglobin and/or methemoglobin in the blood as these pigments have been demonstrated by some investigators. In the vast majority of cases showing cyanosis it is not possible to demonstrate either methemoglobin or sulphemoglobin in the blood by spectroscopic analysis. Marshall and Walzl[13] have shown that the hemoglobin content of the blood in cyanotic individuals is the same when it is determined by the oxygen capacity method as it is when the total iron content of the blood is determined. There was no evidence in most of the cases that they examined that abnormal pigments were present. It was also clear that the blood cells were not interfered with insofar as normal oxygen exchange was concerned. From these observations it was suggested by Marshall and Walzl that the cyanosis and the dark color of the blood when it is withdrawn from a vein is due to a black oxidation product which stains the red blood cells. In view of the fact that abnormal pigments have been found in the blood of some cyanotic individuals and that they may appear soon after the administration of sulphates, such as magnesium or sodium sulphate, it is well to examine the blood of cyanotic individuals for abnormal pigments so that these do not accumulate in large enough amounts to prove deleterious to the tissues. Inasmuch as practically all of the patients receiving sulphanilamide become cyanotic and since there is no evidence that every individual who becomes cyanotic has sulph- or methemoglobinemia, there are no good reasons for discontinuing the drug on account of the presence of cyanosis alone.

Acidosis. One of the changes that take place in the blood following the use of these drugs is the development of a reduced carbon dioxide combining power and the symptoms of acidosis. To prevent this, sodium bicarbonate is usually given at the same time as the sulphanilamide. The precise mechanism by which acidosis is produced is not absolutely clear, although it is known that large amounts of sodium are lost in the urine in these patients.

Hemolytic Anemia. One of the more serious complications that must be looked for is an acute hemolytic anemia. It was first described by Harvey and Janeway,[9] later by Kohn[12] and others, and we have observed 3 cases. From our own experience and that of others the characteristic features of this complication are: (1) a rapidly progressive anemia coming on within 3 to 5 days following the administration of the drug; (2) polymorphonuclear leukocytosis; (3) jaundice and signs of diminished hepatic function in some cases; (4) prompt recovery following withdrawal of the drug, the use of blood transfusions, and forcing fluids to 3000 cc. a day.

The anemia, which is often severe, may develop with great rapidity so that the erythrocyte count and hemoglobin content of the blood may decline to levels of 30 to 40% of normal within a few days after the drug has been started. This decline in the red cells is accompanied by the appearance of anisocytosis, pallor, many nucleated erythrocytes and reticulocytes. The total leukocyte count is usually increased, varying between 20,000 and 87,000 per c.mm. There are many immature neutrophils and myelocytes; platelets are normal in number.

Jaundice has been a feature of most of the patients showing anemia but it has not been present in all. Two of Harvey and Janeway's cases showed no jaundice clinically, although there was evidence of increased blood destruction as determined by the presence of increased urobilinogen in the stools and urine. Bile pigment appears in the urine of some cases and there is evidence of impaired hepatic function as determined by the bromsulphthalein excretion tests. In a case reported by Kohn hemoglobinuria was a feature.

In 1 case studied by us the fragility of the red cells in varying concentrations of salt solution was normal. The Donath-Landsteiner and the Ham phenomena were not present. We were unable to detect any evidence of an intravascular hemolysin. Recovery has followed the use of blood transfusions in all cases, but it is a most serious complication.

In brief, then, one of the complications of this drug is a hemolytic anemia that occurs within the first 5 days following treatment. It can usually be controlled by discontinuing the drug, forcing the fluid intake to 3500 cc. a day, and giving whole blood transfusions. Inasmuch as it can develop rapidly and occur without jaundice, the hemoglobin and erythrocyte count should be followed carefully during the first week of treatment.

Optic Neuritis. Bucy[1] described an isolated instance of optic neuritis occurring in a young girl, aged 16, following sulphanilamide. Vision was reduced for a period of 4 days. There was central scotoma for red and blue and relative scotoma for white. This appeared after the use of one tablet of sulphanilamide, although she had received the drug on several previous occasions for 2 days. Recovery was complete following the withdrawal of the drug.

Skin Eruptions and Fever. Within 4 to 14 days, usually 7 to 10, following the administration of sulphanilamide cutaneous eruptions with fever may appear and persist from 2 to 9 days. The temperature may vary from normal to 106° F., the average being 101° to 103° F., and this may persist from 2 to 9 days, usually 2 to 4. While in about one-half the cases the fever is accompanied by an eruption, it may occur alone without any other signs of toxic manifestations of drug reaction.

The skin rashes have varied considerably and have consisted of urticaria, exfoliative dermatitis, morbilliform eruption, edema of the face and arms, hemorrhagic and purpuric rashes, scarlatiniform eruptions, and in a few cases the eruption appeared only after exposure to sunlight. All of the rashes usually cleared up completely following discontinuance of the drug.

Agranulocytosis. This is a most serious complication of sulphanilamide therapy. With a few exceptions most of the reported cases have ended fatally. Several interesting and important features have been brought out from a study of these cases. The first is that no case of agranulocytosis has been reported as occurring before the fourteenth to the sixteenth day after the onset of treatment. It has also been stated that the leukocyte count frequently drops following the discontinuance of the drug. It is not always clear from the reported cases, however, that the decrease in the leukocyte count occurred in an abrupt manner, since leukocyte counts were not done daily. It is also a striking fact that when death occurred it usually did so within 2 to 3 days after the onset of agranulocytosis. Fatal cases serve to emphasize the importance of making repeated leukocyte counts in all individuals who are receiving the drug for a week or more.

Dosage of Drug. There is no absolute agreement concerning the dosage of sulphanilamide. Most workers have elected to give the drug so that it will be present in the circulating blood in amounts of at least 10 mg. per 100 cc. In general, we have usually given, as an initial dose, 0.6 gm. per kilo of body weight and then followed this dose by 0.6 gm. every 4 hours. In most adults of average weight we have given 8 gm. during the first 24 hours. Usually after that time we continued the drug in daily doses of 4 gm. each. The sulphanilamide of the blood is determined every 2 days during its administration. Hemoglobin and leukocyte counts are done daily. If the concentration in the blood increases above 10 mg. %, the dose is reduced.

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RADIOLOGY

UNDER THE CHARGE OF
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CHRONIC GASTRITIS.

Morgagni (1761) was the first to call attention to gastritis. After him, Broussais (1808) did a great deal of original work on this subject, and in his opinion gastritis was responsible for a number of conditions, such as septicemia, typhoid fever and meningitis; ascites, cerebral hemorrhage and pneumonia were considered by him to be complications of gastritis.

It was not long, however, until it was recognized that Broussais' conception was erroneous; what he had considered to be gastritis was found to be postmortem changes. Beaumont enlarged the knowledge of gastritis by his experimental contributions. The situation underwent a sudden change when Kussmaul invented the gastroscope (1867) and used it in the following year to examine the human stomach. The subject of the experiment was a professional sword swallower. A rigid instrument was used, the lighting was indirect, and no satisfactory view of the stomach was obtained. Mickulicz, about 1881, again attempted gastroscopy with a rigid instrument, but the results were unsatisfactory.

With the invention of the gastric tube, the anatomic conception of gastritis was relinquished in favor of the functional conception. Hypersecretion, hyperacidity, subacidity and anacidity became independent clinical units of what was considered to be nervous dyspepsia (Leube). Achylia gastrica was assumed to be a purely functional disturbance. But the pendulum was found to swing back to the anatomic conception of the disease, and Hayem (1892), by preventing postmortem changes, demonstrated the frequent occurrence of inflammation of the stomach.

Hayem's statements were confirmed by the development of gastric surgery, which furnished a large amount of material for study in the form of resected stomachs. Immediate fixation of resected specimens made it possible to rule out postmortem changes. Later, improved methods of clinical investigation were developed: roentgenology (Rendich, Forssell, Cole, Berg, Gutzeit) and gastroscopy (Schindler, Gutzeit, Korbsch, Henning) contributed greatly to the present knowledge of gastritis.

In a symposium presented before the Radiological Society of North America the comparative value of gastroscopy and Roentgen examination of the stomach was discussed; the theme of the discussion was largely the subject of chronic gastritis. Coincidental with the publication of the papers of this symposium, Ausprenger and Kirklin presented a critical analysis of the roentgenologic aspects of this same subject.

NOTE: A bibliography is appended covering all the references without specific direction as to the individual reference.

Roentgenology is a comparatively new science. It honors the name of the discoverer of the new light which was the foundation of the science. He modestly named it the *x*-ray and this appelation is still more widely used than that of roentgenology and its derivatives. The announcement of the discovery came in an elaborate description of the revolutionary new ray printed in the morning edition of the Wiener Presse. The news was quickly copied by other continental papers and was cabled on the evening of January 6, 1896, from London to most of the civilized countries of the world. The possibilities of the *x*-ray as a diagnostic agent in medicine were discussed before the Berlin Medical Society the day previous to, and before the Society of Internal Medicine in Berlin the day of the announcement of the discovery. By the end of February, 1896, the method was in comparatively general use as a new diagnostic procedure in many countries.

Hemmeter, writing on "Photography of the Human Stomach by the Roentgen Method" on June 18, 1896, quoted Becker as having succeeded in making roentgenograms of the stomach and a loop of small intestine of a guinea pig by distending both with liquor plumbi subacetatis. Hemmeter suggested this same medium be introduced into the viscus by means of a deglutible gutta-percha bag and withdrawn therefrom by aspiration. At that time he did not suggest bismuth, but used it later by intravisceral insufflation.

Loaded tubing passed into the stomach could do little more than outline its greater curvature, but the position of the viscus was thereby roughly estimated.

The suggestion to use the Roentgen method in the study of gastric motor function was made by Bowditch in 1896. Among the first recorded scientific investigation of the gastro-intestinal tract by means of the Roentgen ray were those of W. B. Cannon. His first work on the movements of the stomach was presented before the American Physiological Society in May, 1897. Cats were employed in his researches by Cannon who wrote that "the mixing of a small quantity of subnitrate of bismuth with the food allows not only the contractions of the gastric wall, but also the movements of the gastric contents to be seen with the Roentgen rays in the uninjured animal during normal digestion. An unsuspected nicety of mechanical action and a surprising sensitiveness to nervous conditions have thereby been disclosed." Cannon's preliminary report (May, 1897) antedated the work of Roux and Balthazard on frogs, dogs and man.

In September, 1899, Williams, assisted by Cannon, fed 2 children subnitrate of bismuth mixed with bread and milk and made observations, with the aid of a fluorescent screen, of the movements of the stomach during respiration and of the changes in shape during digestion. In a third child that he examined, using the fluoroscope, he also made roentgenograms at intervals of 1 to 2 hours. Williams observed the intestinal tract using capsules filled with opaque material and the colon with rectum-injected air.

Boas and Levy-Dorn (1896) conducted screen studies, using contrast capsules, and Benedict (1898) observed by fluoroscopic screen the intra-alimentary behavior of capsules containing reduced iron and attempted to localize them by making roentgenograms.

Lester Leonard (1897), by washing out the stomach and introducing bismuth, was able to show, in a case of gastroptosis "the area of the stomach through the bones of the pelvis."

Rieder (1904) advocated in a published paper the ingestion of large doses of subnitrate of bismuth, which he demonstrated to be entirely harmless, as a substitute for artificial insufflation of the stomach with gas, a method not entirely devoid of danger. By means of this method it was possible to demonstrate roentgenographically, in the most detailed manner, the contour, as well as the size, shape and position of the different parts of the gastro-intestinal canal. Moreover, he stated, the motor functions could similarly be studied; according to the experimental work of Pavlow on dogs, the motor movements were the same for bismuth as for milk and water. Rieder prophesied that the extensive use of the Roentgen procedure in the examination of the digestive tract would be of great value in the field of medical practice and would in the future contribute materially to the support of the diagnosis of gastric and intestinal diseases. This work furnished a stimulus to contemporary investigation and sounded an early note of prediction as to the future importance of this function of radiology.

Hemmeter (1906) published the results of his researches. He produced ulcers in rabbits and cats experimentally by creating a defect in the gastric lining and coated the denuded surface with subnitrate of bismuth and, after closing the abdomen, was able to visualize this region by means of the Roentgen ray. He then succeeded in demonstrating such experimentally produced denudations by introducing a bismuth suspension into the stomach of the animal through a tube and studying them by fluoroscopic observation. By having patients drink such a barium suspension, with the stomach empty, he succeeded in visualizing an ulcer in 3 cases; 1 of his patients was operated on and the roentgenologic findings were confirmed.

Reiche (1909) demonstrated an accessory pocket, created by perforation of a gastric ulcer on to the pancreas. He also established the fact of gastric retention to a pathologic degree as a result of gastric ulcer.

Haudek (1910) elaborated upon and popularized the Roentgen method of diagnosis. He verified its practical value in numerous cases that were proved to be correct by surgical investigation or at autopsy. Haudek, and later Eisler, referred to the significance of the spastic contractions of the musculature observed in many cases with mucosal ulceration. These contractions not infrequently led to the development of a functional hour-glass stomach, which existed for years without producing cicatricial contraction.

Forssell (1912) initiated the study of mucosal relief patterns and showed that the rugal folds of the stomach had an independent mechanism, so that they varied from time to time on account of active movements of the mucous membrane itself throughout the entire alimentary canal, and were due to contractions of the muscularis mucosa. These occurred independently of the rhythmic contractions of the muscular coat. Eisler and Link (1921) were able to demonstrate these folds in all normal and most abnormal cases. The exceptions were cases of marked dilatation of the stomach, with excessive hypersecretion, and where infiltrations of the stomach had produced destruction of the mucous membrane.

Schwarz (1908), in order to be certain that the entire stomach, including the pylorus, was completely filled by means of the opaque mixture, determined that the best means of doing this was by demonstrating the presence of the bismuth beyond the confines of the stomach itself. Such evidence would enable the investigator to study the pylorus in its entirety and to prove the absence of obstruction at the pyloric outlet. By working along this line he succeeded in showing the duodenum roentgenographically. He stated that while the first portion of the duodenum could be well filled, the bismuth passed rapidly through the descending and horizontal parts. He also made the highly significant and accurate statement that this first portion of the duodenum was almost the exclusive location for peptic ulcer of the duodenum.

Percy Brown (1933) summarized the foregoing review with these words: "With such a prelude as to alimentary visceral topography, to be amplified soon and later by Cole, Mills, Carman, Le Wald and others, was ushered in the more detailed radiology of the digestive structures, and the field became a lodestone of attraction for the new compass-needle of discovery."

In this field at least two schools of thought and practice developed, one was essential to that of the other, and both to the advancement of roentgenology. One was basically roentgenoscopic (fluoroscopic observation) and depended upon its radiographic records for confirmation. The other founded its diagnostic opinion upon the direct evidence of disease as shown graphically in repeated or seriated exposure records.

Carefully compiled and accurately checked records are available to prove the efficiency of the combined roentgenoscopic and roentgenographic method. A study of these records also reveals that there still remains a field for investigation by other methods with potentials beyond those of the roentgenologic method.

In the successive years of the most recent decade 17% of the total number of patients registered in The Mayo Clinic had symptoms be-because of which they were sent for roentgenologic study of the esophagus, stomach and duodenum. The roentgenologic findings were negative in 11.3% of the total registration (66.3% of those examined). Approximately 7% of the patients with negative roentgenologic findings had surgical investigation for biliary or other tract lesions, many of which frequently produce reflex symptoms in the stomach. In the remaining 59.3% of examined patients showing negative findings the inference remained that their symptoms were due to some reflex cause or some functional disorder; this group would seem to offer the most fertile field for further investigation by such a method as gastroscopy.

The announcement of the Wolf-Schindler flexible gastroscope in 1932 revived interest in attempts to diagnose lesions of the stomach by direct visualization. The flexibility of this new instrument, invented by Schindler, made the procedure relatively easy and safe. Heretofore most physicians felt that the results obtained did not justify the difficulties and the dangers encountered in passing the instrument.

The consensus expressed in this symposium was that the chief value of gastroscopy was in the study of the finer changes in the gastric mucosa; its greatest value probably being in the recognition of chronic gastritis, a definite disease entity in which the changes in the mucosa are smaller than in ulcer and cancer, and, therefore, less easily recognized by Roentgen ray examination. The gastroscopic appearances of hypertrophic gastritis, chronic gastritis with ulcerating erosions and atrophic gastritis were described and said to be typical.

Schindler stated that in most cases the roentgenogram of the gastric mucosa bears little resemblance to the pattern seen by the gastroscopist, and sometimes changes clearly demonstrable at repeated gastroscopic examinations may be entirely imperceptible to the roentgenologist. Conversely, the roentgenologist sometimes sees changes that are invisible to the gastroscopist. He considered gastroscopy as best suited to the study of the mucosa, roentgenology best suited to the study of the gastric tissues.

In Schatzki's experience, a discrepancy between Roentgen findings and gastroscopy was rather rare when changes typical of hypertrophic gastritis were demonstrated by Roentgen examination. The converse was much more common. A large number of patients with an appearance of hypertrophic gastritis by gastroscopy showed a normal Roentgen picture. The changes in these cases apparently involved the mucosa more than the submucosa. Mucosal relief studies by the Roentgen method may suggest a normal stomach where gastroscopy will reveal marked atrophy. Ulcerative gastritis is characterized by shallow superficial erosions; the shallowness of the erosions and the marked degree of accompanying gastric secretion usually prevents demonstration of this lesion by the Roentgen method.

Schatzki summarized the advantages and disadvantages of both methods as he had observed them from the standpoint of the roentgenologist in 7 years' coöperation with gastroscopists. Gastroscopy is by far the best method of examination for gastritis. It is done with precise instruments, such as lenses and mirrors, giving the same optical impression as the naked eye. It is even superior, as it gives a slightly magnified image. Another advantage of gastroscopy is the ability to see colors; additional help is afforded where differences in color are a factor in the making of a diagnosis. The Roentgen examination, on the other hand, is easier to make, less dangerous, and therefore more suited to routine investigation. It is possible to demonstrate all portions of the stomach by the Roentgen method, whereas it is difficult, sometimes even impossible, to see parts of the fundus or the lesser curvature of the antrum by gastroscopy. The routine observation of peristalsis of the whole stomach and the impression obtained by manual palpation which gives information concerning flexibility or rigidity of the wall lend an important advantage to the Roentgen method. Both methods may be combined to advantage in the control gastroscopic examination of the surrounding surfaces and of the crater base to decide the question of malignancy in some ulcers. Gastroscopy is superior in the observation of the final healing of the mucosa in gastric ulcers. In the differential diagnosis between hypertrophic gastritis and diffuse cancerous or lymphomatous infiltrations gastroscopic examination may be an important factor in the final decision. Finally, it is worthwhile to mention that gastroscopic control may correct obvious mistakes in Roentgen ray examination and interpretation.

Kirklin, while welcoming any method that would disclose and identify lesions that escape roentgenologic revelation and recognition, considered the margin of potential improvement to be narrow. The gross lesions, including the advanced cancers and benign new growths, have such striking roentgenologic characteristics, demonstrable even by the simplest technique, that few errors in diagnosis are permissible. The study of the mucosal pattern has long been a part of the standard routine of roentgenoscopy and by it any gastric lesion, whether ulcerative or tumefactive, that visibly alters the internal topography of the stomach is demonstrable even when the diameter of the lesion is only a few millimeters, and any failure to find it should be charged against the examiner and not against the method. Inspection of the duodenal bulb is an essential feature of the gastric examination and cannot be effected with the gastroscope. Gastroscopy as a routine in examination of the stomach will not be warranted until it has been shown conclusively that it is more uniformly accurate in diagnosis than roentgenoscopy and is attended with as little risk to the patient. When medical roentgenology was new it suffered from the enthusiastic claims of its ardent practitioners and its progress was retarded. It was to be hoped that this history would not be repeated in the case of gastroscopy.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 21, 1938

The Effect of Diet Upon Host Resistance to Enteritidis Infection. CHARLES F. CHURCH, CLAIRE FOSTER, and DOROTHY W. ASHER (Department of Pediatrics, University of Pennsylvania, and the Children's Hospital of Philadelphia). The survival curves of groups of mice inoculated with a strain of *Salmonella enteritidis* by stomach tube were reproducible and showed no variation beyond normal statistical error, provided the following conditions were uniform: (1) genetic background; (2) physical environment; (3) diet. Variation in any one of these factors may result in altered survival.

The distribution of the infecting organism in the tissues of mice on the same diet was found to be essentially the same whether the host was of the A-line (90% survival) or the D-line (30% survival). The parasite was found in cultures of the mesenteric glands of both lines, on the second day after inoculation, and successively invaded the spleen, axillary and submaxillary lymph nodes, liver and kidney. The organism was recovered from the heart in 4 out of 20 A-mice and in 5 out of 20 D-mice.

The Steenbock diet and the Sherman diet were found almost equally satisfactory for growth and reproduction of D-mice. However, progenies from mothers on the Steenbock diet showed consistently higher survival following inoculation than progenies from mothers on the Sherman diet. This difference persisted when the young from two maternal diets were changed to the same purified diet beginning 2 weeks before inoculation. Changing the progeny at weaning from the Steenbock to the Sherman diet did not diminish resistance. The diet of the mother during pregnancy and lactation thus appears to be a factor of great importance in influencing the survival of the offspring on exposure to risk of infection.

The Action of Cyanide and of Oxygen Lack on Glomerular Function in the Perfused Frog's Kidney. L. V. BECK and A. N. RICHARDS (Laboratory of Pharmacology, University of Pennsylvania). The oliguria frequently produced in the surviving frog's kidney by arterial perfusion with cyanide-Ringer or with oxygen-free Ringer is, as a rule, not accompanied by a corresponding decrease in arterial perfusion flow. This phenomenon, ascribed by some to depression of secretory processes in the glomerular membrane, has been made the basis of their belief that glomerular urine is a secretion and not a filtrate. Our experiments, like those of Adolph on asphyxia, indicate that arterial vessels which supply glomeruli are constricted by CN or O_2-lack whereas extra-renal vessels (*e. g.*, lumbar arteries, ureteral branches of the urogenital arteries) simultaneously perfused, are not constricted or are dilated. In consequence, glomerular perfusion and glomerular capillary pressure may be decreased by these agencies without corresponding decrease in total arterial perfusion flow and the phenomenon referred to is not inconsistent with the doctrine of glomerular filtration.

Experiments on Water Diuresis. ARTHUR M. WALKER (Laboratory of Pharmacology, University of Pennsylvania). The experiments concerned themselves with the theory that alterations in urine volume are dictated by changes in the production of an antidiuretic hormone by the posterior lobe of the pituitary gland. The results of the experiments were not such as to substantiate the theory.

1. It was found that completely pituitarectomized cats and rats respond to forced water administration and water deprivation by changes in urine volume which are very comparable to those exhibited by the same animals before operation.

2. Gilman and Goodman's finding of an antidiuretic substance in the urine of dehydrated rats (*J. Physiol.*, 90, 371, 1937) is confirmed; but the incompleteness with which rats excrete injected pituitrin, the relative instability of pituitrin in rat urine at pH exceeding 5.0, and the ease with which pituitrin dialyzes out of thin cellophane membranes argue against the substance being derived from the pituitary gland. Further, a similar antidiuretic substance has been found in the urine of pituitarectomized rats and cats and of hydrated rats, cats and rabbits.

3. The subcutaneous injection of water into rats produces a diuresis quantitatively similar to that produced by the oral administration of water in similar amounts. The subcutaneous injection of hypertonic sodium chloride solutions delays or arrests a water diuresis; this antidiuretic effect is shared to some extent by hypertonic glucose solutions but not by solutions of urea, potassium chloride, or sodium chloride.

Localization and Physiological Significance of the Aortic Chemoreceptors in the Dog. JULIUS H. COMROE, JR., and WILLIAM H. F. ADDISON (Laboratories of Pharmacology and Anatomy, University of Pennsylvania). Comparison of the effects of anoxia (produced by N_2O inhalation, intravenous cyanide and lobeline) upon respiration and circulation before and after carotid denervation in 48 dogs showed: (*a*) the intense hyperpnea always produced by these agents was greatly reduced after carotid denervation in 61%; moderately reduced in 28%; only slightly reduced in 11%; (*b*) the hypertension produced by these agents however was invariably intensified after carotid denervation.

This residual hyperpnea and marked hypertension were always abolished by subsequent vagotomy. Even if the carotid innervation was intact, vagotomy alone usually abolished the hypertension produced by anoxia. Therefore, though the hyperpnea of anoxia is produced mainly by carotid body reflexes (and to a lesser extent, aortic body reflexes), the hypertension of anoxia is produced by reflexes arising chiefly in the aortic, and to a lesser extent in the carotid, chemoreceptors. The latter exceptionally produce marked reflex hypertension, but only if the opposing reflex bradycardia is eliminated by vagotomy.

By means of intraäortic injections of lobeline and cyanide, after carotid denervation, the aortic chemoreceptors were localized in the Aortic Body (*Paraganglion Aorticum Supracardiale*). This body (similar in structure to the carotid body) lies on the dorsocaudal aspect of the ascending aorta at the level of the brachiocephalic orifice, and receives blood directly from a short aortic branch. The afferent nervous pathways are over both vagodepressors; electrical stimulation of the fibers to the right vagus reproduces the typical aortic body response —marked hypertension and hyperpnea (similar to that produced by intraäortic cyanide after carotid denervation). Just as the carotid body chemoreceptors are separable from the carotid sinus pressure-receptors, so the aortic body is separable from the aortic arch pressure-receptors. The McDowall reflex may be due to stimulation of the aortic body by anoxia, for these pressor impulses may be abruptly removed not only by vagotomy but frequently by oxygen inhalation.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
JUNE, 1938

ORIGINAL ARTICLES.

PATHOLOGICAL CHANGES PRODUCED BY GASTRECTOMY IN YOUNG SWINE.*

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For a number of years Petri and coworkers[6a,b8–12] have studied the anemia produced in adult dogs following total extirpation or elective resections of the stomach and the proximal part of the duodenum. The original purpose of these experiments was to produce a macrocytic anemia in the experimental animals, but thus far the resulting anemia has been limited to the microcytic variety. When extirpation was limited to the pylorus and the proximal part of the duodenum a non-fatal condition was produced which showed a tendency to remission. These animals showed, as a rule, only large and sharply defined areas of complete loss of hair on the trunk (reminding one of alopecia areata) with pronounced pigmentation of the skin. Achylia and simple anemia were noted. However, when the ventriculus plus the portion of the duodenum containing Brunner's glands was removed in 8 pups (5 to 6 months old) we observed in each a characteristic clinical and pathologic picture. To summarize, these puppies developed extreme emaciation with arrest of growth, salivation, calcium want, coprophagy, muscular atrophy, change in posture (adduction of hind legs, rounded back) and stiff wobbling gait, and a marked degree of simple anemia. In

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* These studies were carried out with the aid of a grant from the Michaelsen Fund.

addition, there developed marked changes in the skin consisting of symmetrical loss of hair, a scaly eczema-like hyperkeratosis, and slight pigmentation. On the other hand, the appetite and defecation were normal. Death occurred as a rule within 4 to 12 months, but 1 animal lived for 19 months. The anatomic lesions consisted of nerve cell degeneration in the central nervous system, spinal ganglia and peripheral nerves, hypoplasia or even aplasia of the bone marrow, and moderate hyperplasia of lymph glands.

This clinical and pathologic picture bears so much resemblance to chronic fatal human pellagra that we have provisionally designated it as "experimental chronic pellagra from extirpation of the stomach" in the dog.

The course of the disease in these animals was not influenced by the daily administration of 10 gm. of yeast extract plus 12 to 18 gm. of "ABC-D inmalt."* On the other hand, the administration of human gastric juice alone gave a prompt improvement in the condition of the animal (especially in the skin). These observations, we believe, demonstrate the presence of an "intrinsic" gastric factor in the puppies necessary for maintaining a normal skin and nervous system.

Experiments[7] were then devised to test this observation in man. A group of patients having chronic endogenous pellagra or "alcoholic" polyneuritis were selected whose condition failed to improve when given an abundant diet plus the oral administration of vitamin B-complex preparations. When human gastric juice (100 cc. 3 times daily), press juice of swine stomach (80 cc. 2 times daily), or a preparation of dried swine stomach (Ventriculin, MCO) was substituted for the vitamin B-complex preparation a rapid clinical recovery resulted except in the mental symptoms.

At about the same time similar therapeutic observations in patients with pellagra or polyneuritis have been carried out respectively by Sydenstricker and collaborators[13] and by Douthwaite,[3] who obtained similar results by administration of human gastric juice in their patients. Thus our view concerning the absence of an "intrinsic gastric factor" in some patients having pellagra and related conditions, based originally on animal experiments, has found support not only in our own observations but in clinical investigations by other observers.

From the findings of our previous experimental and supplementary clinical-therapeutic studies, plus the investigations of Sydenstricker *et al.*, and Douthwaite, we think that the presence of a special factor in the stomach required to maintain a healthy skin and nervous system has been demonstrated in dog and man. Particulars as to its nature and mechanism are not yet definable, although it may properly be designated as a "P" factor. We have found it reasonable to identify it entirely or in part with neuropoietin, one of the components of the antipernicious anemia principle, and consequently to regard some of the clinical symptoms and pathologic-anatomical changes in Addisonian pernicious anemia as etiologically and qualitatively identical with pellagra and polyneuritis. Whether it be justified to group these affections as one neurocutaneous symptom complex is a question that will have to be settled by further clinical and therapeutic investigations.

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* Preparation manufactured by Ferrosan, Ltd. (Copenhagen), containing 1680 internat. units vitamin A, 30 internat. units vitamin B_1, 4 internat. units vitamin B_2, 80 internat. units vitamin C, and 120 internat. units vitamin D per 12 gm.

Because of the therapeutic efficacy of swine stomach preparations in the above mentioned diseases, and in view of our previous experimental results obtained in puppies, it seems natural to expect that swine would prove particularly suitable subjects for further experimentation along these lines.

Studies on gastrectomized swine have been reported by Bence,[1] Maison and Ivy,[5] Goodman and collaborators,[4] and lastly by Waterman and collaborators,[14] aiming chiefly at clinical changes in the hemopoietic system in the direction of pernicious anemia. No skin or nervous signs or symptoms were reported. In our experiments, these changes of the skin and in the nervous system only occurred when the operation was performed in puppies. Therefore we have repeated these experiments in Danish "bacon-swine." The purpose of this study is to demonstrate experimental effects of removal of the "P" factor in another animal than the dog, and compare the pathologic picture produced with similarly produced lesions in the dog and with lesions of pellagra and related conditions in man.

Experimental Conditions. The entire stomach was removed, and esophago-jejunostomy was performed in the swine. At the time of the operation these swine were 6 weeks old. The 6 control and 6 test animals were given the same unrestricted diet plus 12 to 18 gm. of "ABC-D inmalt" and 5 gm. of cod-liver oil daily.

Course of Illness. The animals operated upon appeared normal during the first 1 to 2 months. The appetite was excellent and defecation was normal. Within a couple of months after the operation various changes developed. The pigs showed signs of intense universal itching. They ate the cement of the pen in which they were confined (calcium want?). A pronounced inhibition of growth gradually assumed the character of complete arrest of growth, finally becoming extreme emaciation (Fig. 1). The hair of the animals was lost in part, the remaining hairs became long, and lost its lustre, reminding one of sheep's wool; a layer of brownish oily material was deposited on the skin. In some cases, the skin showed flat, rather large, warty plaques; but, in contrast to the previous experiments on dogs, pigmentation of the skin was not observed, perhaps because the pigs were penned up with but little access to the open air. The shape, posture and gait of these pigs were gradually altered; the hind legs appeared relatively long, the back was markedly bent, and the gait became stiff and staggering. There appeared to be some muscular atrophy of the extremities. In the last months of the experiment there was a pronounced involvement of the central nervous system, manifesting itself by almost permanent fibrillary twitchings, contractures of the extremities, localized spasms, and almost ataxic gait. Diarrhea developed terminally. There further appeared a very severe degree of microcytic hypochromic anemia. Hyperglobulinemia was demonstrated in 2 animals. The animals died suddenly, sometimes following a brief period of somnolence, after an observation period ranging from 13½ to 17½ months. In these experiments, the fully developed chronic disease was not influenced in general by administering liver extract* intramuscularly or by stomach preparations *per os*. Following administration of these preparations, as reported in a previous paper, a pronounced reticulocyte response was noted which was not followed by improvement in the degree of anemia.

Pathologic-anatomical Changes. On autopsy, these animals presented in composite a large number of changes, forming a rather varied picture.

The common macroscopic changes observed include arrest of growth, anemia, emaciation, complete loss of adipose tissue, moderate muscular atrophy, and changes in the skin, involving loss of hair. In addition, there was atrophy of the thyroid, and slight chronic inflammatory changes in the mucous membrane of the tongue. The site of the esophago-jejunostomy had healed well, presenting no dilatation, nor any remnants of gastric mucosa worth mentioning.

The microscopic changes in the nervous system of the gastrectomized pigs were qualitatively alike, but quantitatively variable. They were conspicuous in the central nervous system and the spinal ganglia (Fig. 2), but less pronounced in the peripheral nerves. The changes consisted of various degenerative phenomena in the nerve cells, *e. g.*, vacuolization of the protoplasm, alteration of the Nissl structure, eccentric position of the nuclei, or even karyorrhexis. In the nerve fibers the myeline degeneration was of a diffuse character but of slight degree. Finally, there was a conspicuous dilatation of the small blood-vessels (Fig. 3) with thickening of their walls. These findings, on the whole, corresponded to those found in gastrectomized puppies.

In a majority of these animals the spleen had undergone atrophy. The lymph glands contained a good many plasma cells or eosinophil leukocytes, but were not enlarged. The bone marrow was gelatinous, red in color (in the femur) or grayish-yellow (in the tibia). On microscopic examination, the marrow was found to be markedly

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* Hepsol Fortior, manufactured by Medicinalco, Ltd. (MCO), Copenhagen.

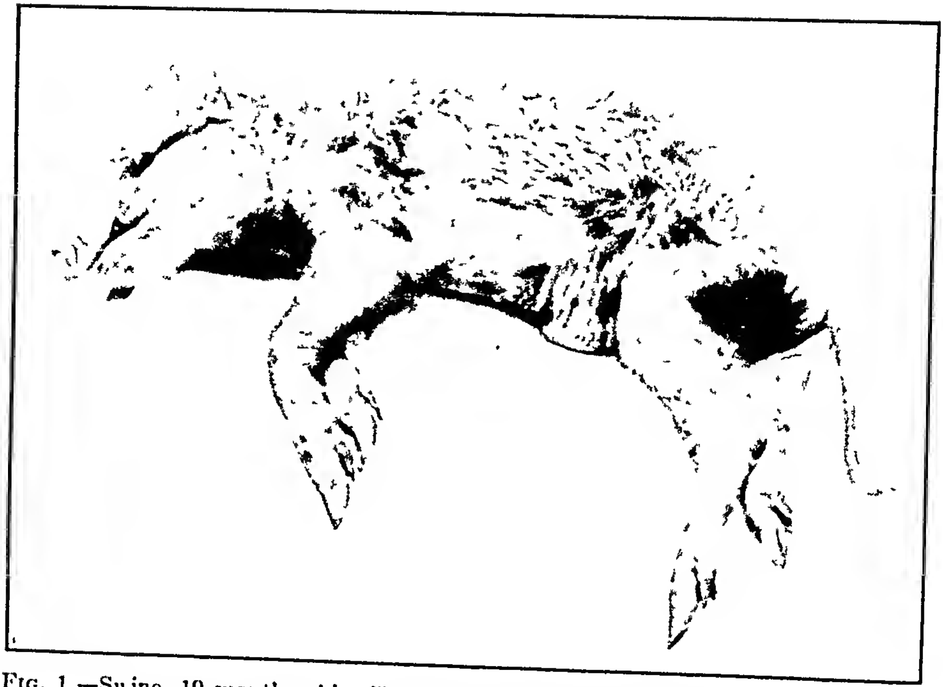

Fig. 1.—Swine, 19 months old. Total gastrectomy at age 6 weeks. Observation period 17½ months. Weight, 16 kg. Length of trunk, 65 cm.

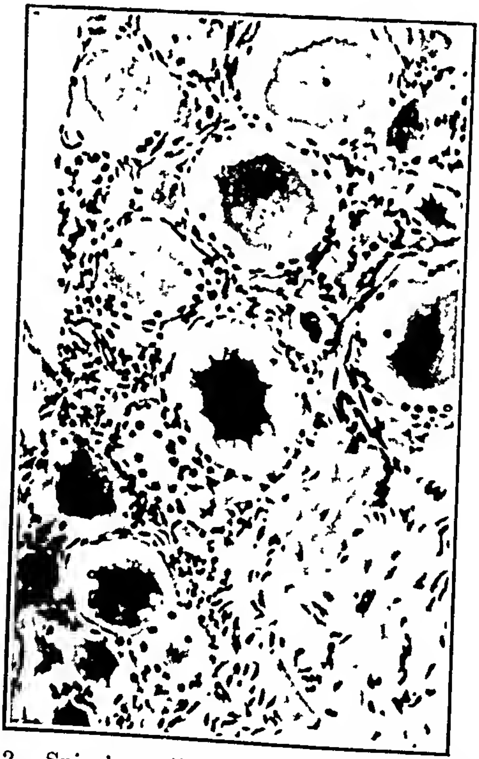

Fig. 2.—Spinal ganglion from gastrectomized swine.

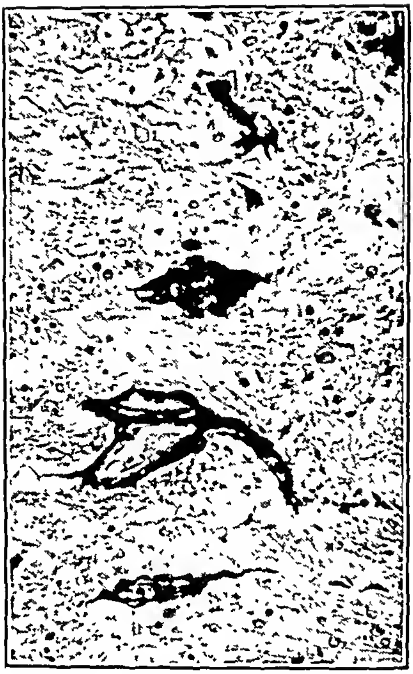

Fig. 3.—Spinal cord of gastrectomized swine, showing dilatation and thickening of central blood-vessels.

edematous, with dilatation of the blood-vessels. The number of cells in the marrow was variable in the individual animals; the femur showed a "fat" marrow rich in cells, while the marrow of the tibia was almost free from specific cells. The number of specific bone-marrow cells was rather scanty, with a distribution corresponding to that observed in adult animals. Nucleated red cells were relatively few in number.

A minority of these animals, on the other hand, presented a moderate or marked hyperplasia of the spleen and lymph glands. These organs showed a marked plasma-cell metaplasia and a more scanty number of myeloid elements. In 1 animal, the bone marrow was the site of diffuse fibrosis with scattered small islands of marrow cells; another animal showed a diffuse marked hyperplasia of the bone marrow, though without any pronounced predominance of nucleated red cells. The latter animal showed also cirrhosis of the liver, of "Hanot's" type. It was in the 2 latter animals that hyperglobulinemia was encountered, and in these the inhibition of growth was distinctly less pronounced than in the other animals.

Finally, other special changes were seen in 1 or more of the 6 animals in this group, namely: tendency to transudation (subcutaneous edema, hydrothorax, ascites), hypertrophy of the heart, hyaline degeneration of the glomeruli of the kidneys, cellular infiltrations (presumably myeloid) in the testis and liver (partly with beginning cirrhosis?), hyperkeratosis, and marked osteaporosis.

Discussion. By removal of the stomach in young pigs it is possible to produce a number of diverse, severe, clinical and pathologic-anatomical changes. The picture is characterized in particular by arrest of growth, skin changes, hypochromic microcytic anemia, and degenerative changes in the central nervous system.

The present experiments have afforded an additional proof of the far-reaching significance of the stomach to the organism, especially during growth, indicating the presence of a specific "P" factor in the stomach concerned with maintaining a healthy skin and nervous system. Whether, for instance, the coincident abolition of the hydrochloric acid production directly or indirectly plays a part in the development of some of the diverse changes here observed is a question that remains open for the present. In their features and course, the changes observed in our pigs deviate in nearly every respect from the findings reported by other investigators in experiments with a similar technique. This difference no doubt is attributable to the young age of our pigs at the time of the operation.

Young pigs, like ours, may safely be characterized as suitable experimental subjects for further studies on the relation of the stomach to the changes in the skin and nervous systems, as in pellagra, and may supplement our knowledge of the relation of the stomach to pernicious anemia, as well as on the pathogenesis and possible etiologic explanation of several of the concomitant phenomena here observed. In addition, the experimental and clinical-therapeutic studies we have carried out thus far illustrate the general risk to the organism that may be involved in extensive resection of the stomach, especially in relatively young patients.

The condition of hyperglobulinemia with preponderant plasma-cell metaplasia of the spleen and lymph glands as observed in 2 of our animals lends experimental support to the hypothesis advanced by Bing and Plum[2] concerning the causal aspects of the hyperproteinemias. Finally, in view of the reticulocytic reaction which the animals have shown to administration of liver and stomach preparations, as mentioned in a previous paper,[9] our experiments suggest the possibility of elaborating a biologic method for determination of the potency of "antipernicious" preparations and their possible variations in action.

Summary. Operative removal of the stomach in 6 pigs, 6 weeks old, gives rise to a number of severe clinical and pathologic-anatomical changes that may be interpreted as phenomena similar to those found in human pellagra. Conspicuous features in this condition are arrest of growth, hypochromic microcytic anemia, and extensive changes in the skin and in the central nervous system. In addition, there were inconstant diverse changes, as hyperproteinemia, plasma-cell metaplasia of the spleen and lymph glands, cirrhosis of the liver, osteoporosis, and other phenomena.

In principle, the results of these experiments correspond to our findings in previous studies on pups, further suggesting the presence of a specific factor in the stomach of swine, dog, and man which is required to maintain the skin and central nervous system in a normal healthy state.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

IV. THE PRIMARY ROLE OF THE PLASMA PROTEINS IN CONDITIONING WATER RETENTION AND EDEMA FORMATION IN NORMAL AND "TOXEMIC" PREGNANCY.*

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THE importance of water retention in "toxemia" of pregnancy has been previously emphasized.[6a,b,c] This condition is, of course, to be *differentiated from vascular or renal disease associated with* pregnancy. It has been pointed out that "toxemic" manifestations may be relieved by decreasing water retention[6a] or exaggerated by inducing further water retention.[6b]

Previous observations[6a,b,c] indicated that the chief factor responsible for water retention in pregnancy is a lowering of the colloid osmotic pressure of the plasma due to hypoproteinemia. However, in view of the rather widely held beliefs that water retention in pregnancy depends upon hormonal[1] or renal[9] disturbances, the present study was undertaken to establish conclusively that it is the plasma protein level which is the primary and most important factor involved in water retention in both normal and "toxemic" pregnancy.

The presence or absence of gross edema is an extremely crude measure of water retention. It is well known that one individual may show visible edema following the retention of only 2 or 3 kg. of water, whereas another patient may conceal in the body tissues 5 or 6 kg. of retained water. The literature contains many references to a so-called critical level of the plasma proteins, below which edema occurs. The recent studies of Weech and his associates,[7] however, indicate that water retention proceeds uniformly *pari-passu* with the decline in the plasma-protein level of dogs on protein-deficient diets and that the first appearance of manifest edema is not associated with any sudden or marked increase in water retention.

The evidence in favor of hypoproteinemia as the chief cause of water retention in pregnancy may be summarized at this point. 1, The amount of water retained by pregnant women during the administration of sodium salts[6b] is inversely proportional to the colloid osmotic pressure of their plasma proteins.[6c] 2, Pregnant

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* This study was aided in part by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

women with hypoproteinemia, even though they have no manifest edema, lose weight readily ascribable to water loss when placed upon a diet containing daily 260 gm. of protein and an adequate number of calories.[6a] 3, It has been determined by an analysis of data[6a] that the amount of body weight lost is very roughly in inverse proportion to the level of the colloid osmotic pressure of the plasma proteins. The lack of better correlation may be ascribed, among other factors, to the absence of a preliminary period of stabilization following admission to the hospital, to the absence of any control of the salt intake, and to the fact that at the time the observations were made, the chemical methods used to determine the quantitative amounts of plasma albumin and total protein were by no means as uniformly accurate as at present. Further, blood was withdrawn for these determinations on the patient's first day in the hospital, whereas for the data to be presented here it was not taken until the patient had become stabilized as far as fluid exchange was concerned after several days on the hospital ward.

Methods. Twenty women in the last trimester of pregnancy were selected for study. They included 3 normal pregnant women and 1 each diagnosed as having chronic glomerulonephritis, acute pyelonephritis, chronic pyelonephritis and polycystic kidneys; 8 women had essential arterial hypertension and 5 "toxemia" of pregnancy. Upon admission to the ward the patients were placed upon house diets without restrictions of any sort. They were not confined to bed. Salt and water were permitted *ad lib.* No sodium bicarbonate was allowed, nor were saline cathartics permitted, since it has been shown[3] that at least magnesium sulphate may act as an acidifying diuretic in patients with edema. The patients were weighed each morning before breakfast. The arterial blood pressure was measured after the patients had been at rest in a chair for 20 minutes. Blood was not withdrawn for the determination of the plasma proteins *until the third or fourth morning in the hospital,* when *the patient's weight* had become relatively constant. The women were recumbent for at least 20 minutes before the blood was withdrawn without stasis from an antecubital vein. The venous pressure was determined at the same time by the method of Moritz and von Tabora. By a micromodification of Howe's method the plasma albumin and the total plasma protein concentrations were determined on blood to which a uniform amount of potassium oxalate had been added to prevent coagulation. It is believed that all of the above precautions are essential if quantitatively accurate results are to be obtained. After the preliminary period of observation was completed each patient received 1500 cc. of skimmed milk daily for 5 days as the only food. Each was encouraged to take whatever water she desired. No limitation or forcing of fluids was permitted. The skimmed milk régime was employed because it was *par excellence* an ideally uniform, low-sodium diet. Other types of low-sodium diets are likely to be unpalatable and therefore variations in food intake (and hence salt intake) occur. Furthermore, none of the patients seriously objected to this régime, nor did disturbing symptoms from lack of food occur. Fifteen hundred cubic centimeters of skimmed milk contain approximately 0.57 gm. of sodium, 2.14 gm. of potassium, 2.14 gm. of calcium and 0.18 gm. of magnesium, together with 53 gm. of protein, 73 gm. of carbohydrate and 10 gm. of fat, with a total of 600 calories. The choice of a low-sodium régime was, of course, based on the previous observation that the administration of sodium in excess resulted in water retention.[6b]

Results. Each of the 20 women lost weight during the period of 5 days when they had only milk. In the chart is shown the percentage of the original body weight which was lost. This was calculated by subtracting the weight on the morning of the sixth day from the weight on the morning of the first day of the skimmed milk régime and dividing the result by the latter weight. The percentage weight loss for each patient has been plotted against the calculated colloid osmotic pressure[8] of that patient's plasma proteins. The correlation is remarkably good, and establishes the primary importance in these 20 women of the plasma-protein level in conditioning water retention. In every instance in which visible edema was present this disappeared. It is, however, worthy of note that some patients without manifest edema lost as much as 8 pounds of weight, apparently water.

In the 12 patients who were diagnosed as having primary vascular or renal disease and in the 3 normal women no consistent effect of that milk régime upon blood pressure, albuminuria, or symptoms was noted. In the 5 patients with "toxemia" of pregnancy, symptoms such as headache and visual disturbances abated, the blood pressures returned to normal and albuminuria decreased. These latter women were placed on a relatively salt-free, 150-gm. protein diet following the skimmed milk régime. Under this therapy they continued to remain free of edema and "toxemic" signs and symptoms. Studies made 6 or more weeks postpartum failed to reveal evidence of vascular or renal disease. On the other hand, the 12 women considered to have vascular or renal disease during pregnancy all continued to show hypertension or urinary abnormalities later.*

Complete data on the relation of water retention to arterial hypertension in pregnancy will be reported at a later date.

Discussion. These 20 patients' food contained daily only 600 calories. One must thus ask how much of the weight loss in 5 days may be ascribed to the burning of body fat. Such loss depends upon the weight of the patient and the total metabolism. The total metabolism of patients at rest on a hospital ward can hardly be more than basal +20%. Pregnancy raises the metabolism by approximately an additional 20%. To insure against underestimation, calculation of the *theoretic* weight loss from the burning of body fat in these patients has been made on a basis of basal requirements +60%. Nineteen of these 20 women weighed between 120 and 170 pounds. A 600-calory intake for 5 days should theoretically result in a loss of 1.47% weight in a 120-pound subject and a loss of 1.66% weight in a 170-pound subject from the burning of body fat. Since the difference is but 0.19%, it is apparent that this factor does not enter into the great differences in the amounts of weight lost by these subjects, and that at most it can account for less than 2% of the total weight loss. Further, these patients showed no tendency to regain their lost weight when placed on sodium-poor but adequate caloric diets. Two patients, not included in this report because they were not placed on the skimmed milk régime, were, however, given relatively sodium-free diets containing adequate calories. Each lost essentially the same amount of weight as did patients on the milk régime with similar plasma osmotic pressures. Lastly, 1 patient who lost 6.3% of her body weight on the milk régime was allowed to partake of a house diet with sodium chloride taken freely. After she regained her original weight she was again placed on the milk régime, but with 6.3 gm. of sodium (as the bicarbonate) added. Only 0.9% of weight was lost in this 5-day period.

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* Since this paper was submitted for publication 22 additional pregnant women have been studied, 10 of whom had "toxemia" of pregnancy. These 10 women all showed a return of blood pressure to normal and a subsidence of "toxemic" symptoms concomitant with the loss of retained water, while the 12 women with primary vascular or renal disease showed no consistent change.

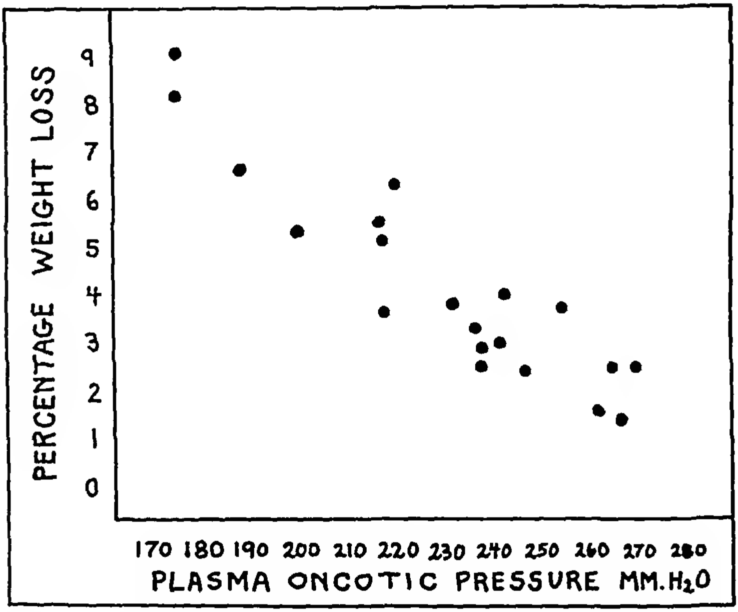

CHART I.—Percentage weight loss in 5 days during the administration of 1500 cc. of skimmed milk daily plotted against the colloid osmotic (oncotic) pressure of the plasma proteins.

It is thus apparent that the weight losses observed in these patients represent essentially a loss of retained water, and that the amount lost is a measure of the amount originally retained.

Much has been written concerning the rôle of the pituitary antidiuretic hormone in inducing water retention in pregnancy.[1] More recently other hormones[4] have been shown capable of causing changes in water metabolism. No proof has been offered which has withstood critical examination that any hormones are involved in water retention in pregnancy. Certainly the data here presented do not require the assumption of hormonal influence. It is known that anemia *per se*, irrespective of the plasma protein level,[5] can condition water retention. One of the patients in this study was observed twice on a skimmed milk régime. During the first period (not included in this report) her hemoglobin was 37% (Sahli) (5.76 gm. per 100 cc.). She lost 8% of her body weight in 5 days and her diffuse generalized edema disappeared. The plasma-protein level at this time was such that the calculated osmotic pressure was 251 mm. of water. Later, when after treatment as an out-patient her hemoglobin was 72% (11.2 gm. per 100 cc.) she returned with a calculated osmotic pressure of 237 mm. of water but no edema. This time she lost only 3.3% of body weight while taking for 5 days a diet consisting only of 1500 cc. of skimmed milk.

It is also well known that hypoproteinemic water retention, both in animals and humans, may not be amenable to therapy either by sodium withdrawal or acidifying diuretics if the level of the plasma proteins is exceedingly low. A patient with "toxemia" of pregnancy and a calculated osmotic pressure of but 150 mm. of water lost only 3% of body weight on the skimmed milk régime and only 1% additional when ammonium chloride[6b] was added. She continued to have generalized edema, hypertension and other toxemic symptoms. Labor was induced. Six weeks later her weight was 38 pounds less, edema absent, blood pressure normal, and urine free of albumin.[*]

There is no question but that acute glomerulonephritis and probably certain other rare types of renal lesions may result in edema apart from an effect on the plasma proteins. However, acute glomerulonephritis has an incidence of less than 1 in 5000 pregnancies.[2] None of the patients reported here suffered from this condition. Furthermore, the edema fluid of acute glomerulonephritis has a high-protein content whereas the edema fluid of pregnancy toxemias is of low-protein content.

The patients suffering from acute pyelonephritis, chronic pyelonephritis, polycystic kidneys and glomerulonephritis each lost weight in proportion to their plasma-protein levels. It is, therefore, apparent that at least in these 4 patients water retention was unrelated to the renal condition except insofar as the latter affected the plasma-protein level.

An elevated intracapillary pressure brought about through arteriolar dilatation from a lack of vitamin B_1 as in beriberi may be accompanied by edema. That this is not the cause of edema in pregnancy toxemias has been indicated in the preceding paper.[6c] Likewise an increased intracapillary pressure due to a large increase in venous pressure as in congestive right heart failure may cause edema. Data on patients with heart failure have not been included in this report. No patient had a pressure in the antecubital vein greater than 15 cm. of water.

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[*] Two similar patients have been observed since this paper was submitted.

The rôle of increased venous pressure in the legs during the last trimester of pregnancy in producing local edema is obvious. Many pregnant women will lose weight upon being put to bed and some merely through a restriction of activity, presumably from alteration in the femoral venous pressure. There is no doubt that ambulatory hospital existence represents a definite restriction of activity, but this is of no concern in connection with the observations reported here because the same restriction of activity was present during the preliminary control period.

It is thus apparent that in the absence of severe anemia, congestive heart failure and acute glomerulonephritis, water retention in both normal and "toxemic" pregnancy depends essentially on the level of the plasma proteins and may be influenced, as in non-pregnant patients and laboratory animals, by changes in the intake of electrolytes, chief of which is sodium. Thus, water retention in pregnancy does not differ from water retention in the non-pregnant.

Conclusions. 1. Whether there is manifest edema or not, water retention is nevertheless present in greater or less degree in a large proportion of women during the last trimester of pregnancy. It may amount to as much as 10% of body weight.

2. This water retention is primarily conditioned by the level of the plasma proteins. The amount of water retained is in inverse proportion to the osmotic pressure of the plasma proteins.

3. Unless the plasma proteins are below a certain level, a régime consisting of 1500 cc. of skimmed milk daily, and hence extremely low in sodium but relatively high in calcium and potassium, will result in the elimination of retained water.

The writer is indebted to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital for their coöperation which made this study possible.

Miss Margaret A. Adams performed the chemical determinations reported in this paper.

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THE SEDIMENTOMETER.

A PHOTOGRAPHIC RECORDER OF THE SUSPENSION STABILITY OF THE ERYTHROCYTE.

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The erythrocyte suspension stability test has long passed the initial experimental stage and is now recognized throughout the world as a routine laboratory investigation of practical service to medical clinics. In many articles favorable reports will be found on its value in tuberculosis,[12] rheumatic carditis,[1] rheumatoid arthritis and allied complaints, syphilis, various infective conditions and gynecologic lesions.[3] Frequent repetition of the test is advisable and it then becomes a reliable indicator of the changing reactions of the patient to infective processes. Thus in pulmonary tuberculosis Trail[11] has found the repetition of sedimentation tests at regular intervals to be of considerable value in assessing the prognosis of sanatorium cases, and other writers[4] have confirmed the abnormal sedimentation rate in afebrile tuberculous patients with slowly progressive disease. It is owing to its extensive use that the erythrocyte sedimentation test has been made as simple as possible by making a single observation at the end of 1 hour's sedimentation. On the other hand, it is realized that to obtain more accurate information it is necessary to take frequent readings. Thus Cutler[2] in particular stresses the importance of observing the rate of sedimentation in the early stages; this he achieves by recording readings every 5 minutes; the results are then recorded in the form of a graph, an impressive picture being obtained of the rate of fall of the cellular element of the blood.

Such a sedimentation test, involving personal readings every 5 minutes, though simple enough to perform, takes up much of a clinician's time, the more so if it is to be frequently repeated. It is not surprising that mechanical devices have been made to record result automatically.[7] But so far as the writer is aware these have not been sufficiently practical to be widely used; thus Sulkowitch[10] devised an apparatus which worked by throwing a shadow outline of the sedimenting blood on sensitized paper mounted on a kinographic drum. Using a somewhat similar apparatus the author was confronted with practical difficulties. As the beam of light traversed the clear plasma layer above the sedimenting blood, diffusion of this light often gave a poorly defined silhouette. In addition, the standardized electric light had to be carefully controlled so that it was necessary to place the apparatus in a light-proof compartment in order to exclude daylight. The instrument was thus made bulky while the need both of a dark room for loading and of a mechanism for automatic switching off the light at the end of the exposure period added further complications. On the other hand, such an apparatus takes a continuous record from a number of sedimentation tubes. Other investigators[9] now photograph a number of tubes at the end of a convenient time period. This method requires a short focusing camera and a special mechanism for operating the lens shutter. Ride,[8] using a Leica camera, has made an apparatus which takes multiple pictures at 6-minute intervals. Judging from his brief description the mechanism must be costly and in order to obtain consecutive recordings of the individual tubes, each photograph must be read in turn and the results plotted on graph paper. The author has combined both the silhouette and camera methods to produce a compact instrument in which many of the advantages of both methods are included.

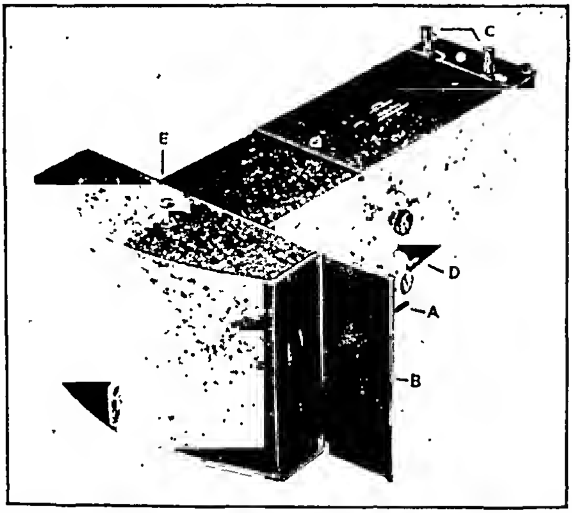

Fig. 1.—The sedimentometer. The photographic plate is loaded through the door (*B*) into the moving stage (which can be seen just to the left of the door). This stage is caused to move by releasing the pin (*E*), and the image of the tubes (*C*) is received on the photographic plate when the shutters (*D*) are opened.

Description of Sedimentometer. As previously described,[5] the new apparatus known as the "sedimentometer" (Fig. 1) actually photographs the sedimentation tube on a moving light sensitive surface. To achieve this, light obtained from any reasonable source, including daylight, passes through a frosted glass window in the sedimentometer. It then falls on a slot holding the sedimentation tube. The light is readily transmitted through the clear plasma layer but is blocked out by the opaque mass of red cells below. Behind the sedimentation tube is a single lens; this throws an image of that part of the tube above the sedimenting cellular layer on to a light sensitive surface behind a narrow vertical slot at the back of the apparatus. On making a short exposure a narrow vertical

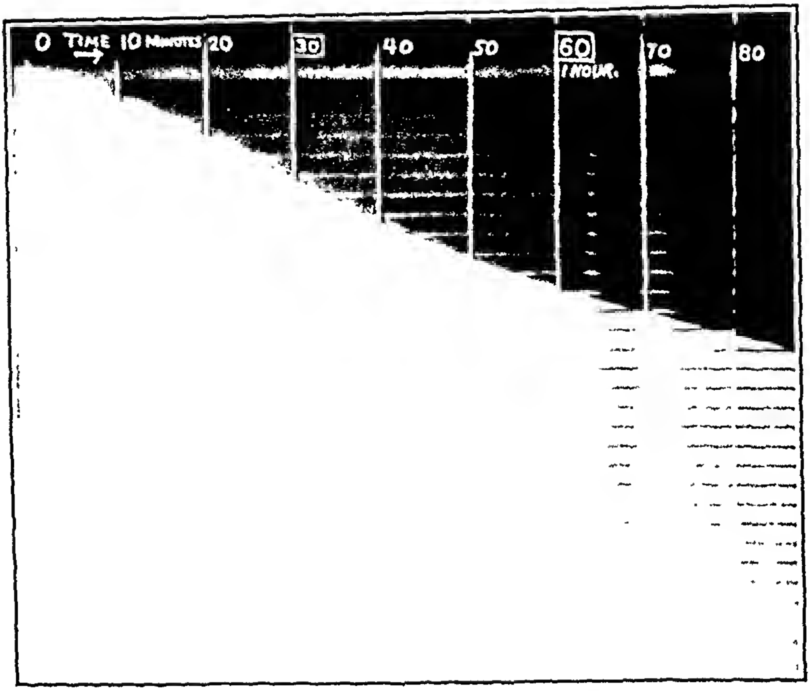

FIG. 2.—Photograph of a sedimentation curve taken over 90 minutes. Sedimentation index, 11 mm.

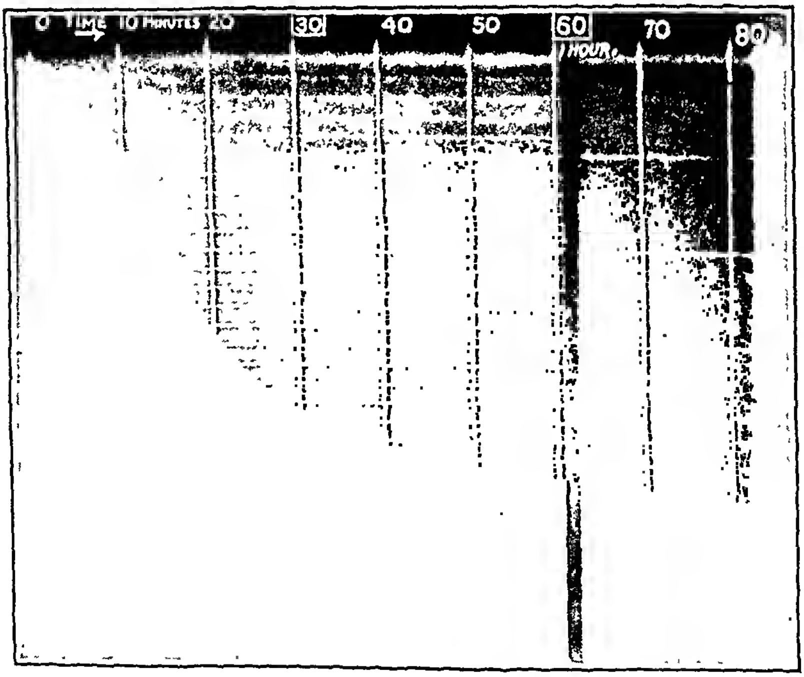

FIG. 3.—A vertical curve. Sedimentation index, 22 mm.

photograph is obtained. This will show a small free space above the fluid level; immediately below that the meniscus will be seen as a thin white line. Beneath the meniscus is the clear plasma layer with the millimeter graduations of the sedimentation tube showing through. Finally, a sharply defined margin accurately indicates the upper surface of the opaque cellular layer. But to obtain a continuous record of the blood fall, the photographic paper must be mounted on a moving stage. A simple clockwork mechanism drives this stage which carries an ordinary camera-plate holder loaded with photographic paper. Thus in the sedimentometer, coincident with the [illegible] in the tube, sensitized paper will travel past the tube image which can only fall on the paper through the vertical light slot. A continuous and accurate photosedimentation graph is thus obtained. In the standard machine, during the short time required for preparation of the specimen and withdrawal of the covering slide of the plate holder, the movable stage is kept locked at zero position, but on closure of a side-door movement of the stage commences. It then travels at a rate of 60 mm. an hour. The author now records time markings by placing a transparent piece of film in front of the sensitized paper when the plate holders are loaded. Opaque vertical lines are drawn on this film so that every 10 minutes one of these passes the light slot. After development not only are the millimeter graduations of the tube recorded but also these time markings, so that the print is actually a completed graph (Fig. 2). Retouching is therefore unnecessary.

A sedimentometer may be built to record any type of tube, but for compactness, shorter tubes of 50 mm. or less in length are the most suitable. This Cutler technique[24] has been adopted as a standard. By projecting an image twice the actual size on to a stage moving at a rate of 60 mm. an hour, the photosedimentation curve will conform to the recognized Cutler standards. Speed and magnification can, of course, be varied. In a multiple sedimentometer 4 Cutler tubes can be recorded on quarter plate size paper; then the images would have to be the same size as the tubes and the stage made to travel at the rate of 30 mm. an hour. The resultant curves, though smaller in size, would be proportionally identical with those of the standard sedimentometer. By use of the formula $D = 2/3\ LM$ (where D equals the distance traveled by the stage in an hour, L the length of the tube, and M the magnification) any of the shorter tubes will give approximately the same results. For tubes longer than 50 mm., however, this formula needs slight modification.

Discussion. A comparative study of sedimentation graphs from tubes of different lengths will help to explain the variations of their respective curves. The typical vertical curve of Cutler (Fig. 3), indicating very rapid sedimentation, consists of a short pre-sedimentation period when the fall is very slight, a true sedimentation period of rapid fall, and finally a packing stage when the curve flattens out. In a longer tube the pre-sedimentation period is approximately the same, but the sedimentation period is continued almost throughout the whole hour and to obtain a packing stage proportionate to the Cutler curve, observation must be continued beyond 1 hour. To apply it for longer tubes, the above formula is therefore modified by not only increasing the time of exposure but also by causing the stage to move at a slower speed. In the case of a 100-mm. tube,[13] when using a magnification of 1, the time of exposure should be 90 minutes and in that time the stage should travel 60 mm. If curves of 50- and 100-mm. columns of the same blood are superimposed in this manner, they will be found more or less to coincide (Figs. 4 and 5). As the pre-sedimentation time is approximately the same in both tubes, the vertical curve in the

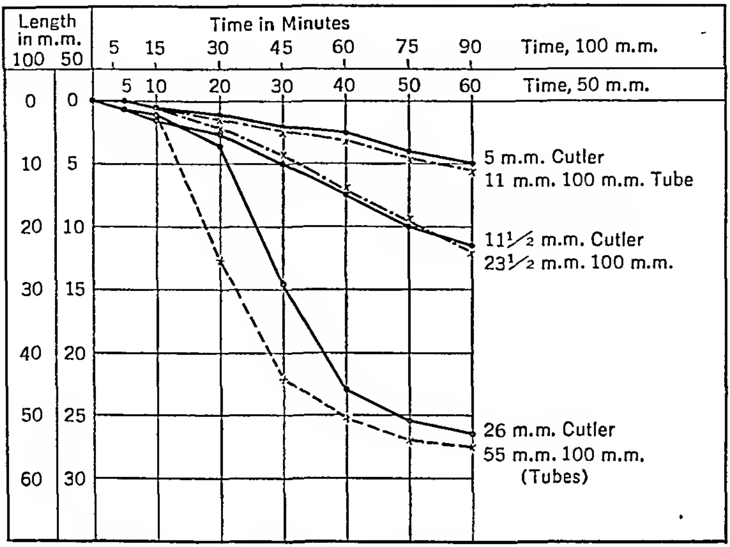

FIG. 4.—Sedimentation curves of three different samples of blood to illustrate text. The unbroken lines represent the 50 mm. curves and the interrupted lines the 100 mm. curves.

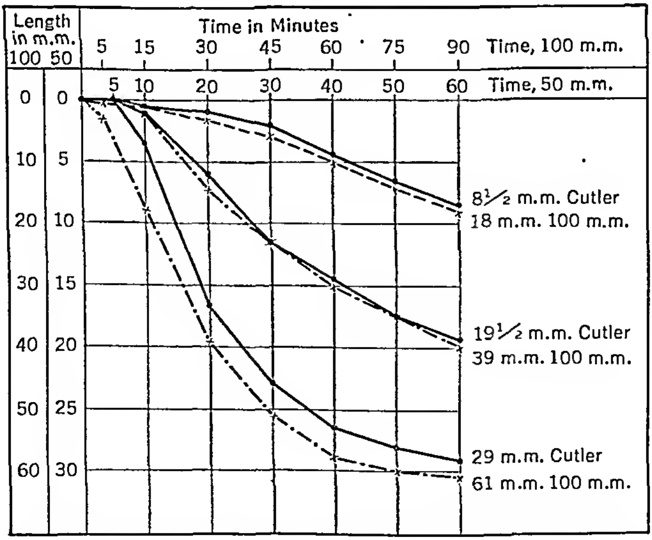

FIG. 5.—Sedimentation curves drawn as in Fig. 4. Note that the 100 mm. vertical curve is here much steeper than the 50 mm. curve.

case of the longer tube will be much steeper (Fig. 5); this should prove rather advantageous. The readings in the graphs shown were obtained by an observer before any such relationship was thought of, and the records are taken at random from a series of 10 samples. It is possible that by further increase of the exposure period any length of tube greater than 100 mm. may also be used. Hitherto there has been much confusion owing to inability to compare the results obtained by different methods, but with the introduction of the sedimentometer, it is possible in most cases to record curves that will conform to those standardized by the Cutler technique. Furthermore, it is hoped that the instrument will be of some value in introducing the erythrocyte suspension stability test as a routine in medical clinics, especially tuberculosis dispensaries. Judging from a small personal series of repeated sedimentation tests performed on over 100 tuberculous patients, all of whom were kept under close supervision (including physical, bacteriologic and radiologic examinations), the Cutler method has been found to correspond accurately to the clinical conditions of the patient. Again and again a fall in the sedimentation curve has been found to herald a bout of activity. Because of this close correlation, the Cutler method has been adopted as a standard in the sedimentometer.

Summary. The value of multiple readings when observing the suspension stability of the erythrocyte is emphasized and the need of an apparatus for automatic recording suggested.

The working principles of such instruments that are at present used in laboratories are briefly outlined. For convenience these are referred to as the silhouette and camera methods.

A new and compact apparatus known as the "sedimentometer" is described. This gives a continuous photosedimentation curve which conforms to recognized Cutler curves. The essential modifications are described to indicate how the sedimentometer may be used to record the suspension stability test in tubes of varying lengths.

The author is indebted to Dr. McDougall, Medical Director of Preston Hall, for permission to use the readings published in this article. He is grateful to Drs. J. C. Crawford and W. E. Fitzgerald, also the Ellis Optical Company (the manufacturers) and others, for their helpful suggestions; and to Messrs. Hawksley & Sons, Ltd., of 17, New Cavendish Street, London, W.1., the distributors of the sedimentometer.

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THE INFLUENCE OF ANEMIA ON BLOOD SEDIMENTATION.*

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For some years there has appeared an increasing number of papers on blood sedimentation, emphasizing the necessity of correcting for anemia to make possible a more accurate evaluation of the sedimentation test. Those who advocate "correction" maintain that anemia materially increases the sedimentation rate, so that the latter reflects not only the activity of the disease but also the cell concentration. They further assume that the anemia factor can be isolated and corrected for by simply subtracting sufficient plasma to bring the volume percentage to 47% or the cell count to 5,000,000 before performing the test. The difference between the sedimentation rate of the corrected and the uncorrected or anemia sample is believed to represent the increased sedimentation brought about by the anemia factor itself. Formulæ have been proposed and graphs and tables constructed in an attempt to simplify the computation of just how much of any particular sedimentation rate is due to the associated anemia.

The present study was undertaken to determine the justification of current efforts to correct for anemia. The answer is best sought in an understanding of the mechanism of blood sedimentation.

Blood Sedimentation and Rouleaux Formation. Although the mechanism of blood sedimentation is only partially understood, certain facts are available. Suitable experiments easily show that the plasma, or the medium in which the cells are suspended, is primarily responsible for the rapid settling, and not the number, size or shape of the erythrocytes. The rate of settling can be controlled at will by altering the suspension medium, thus showing that the cells play only a passive rôle.

When the behavior of settling cells is studied under different conditions the essential difference is that those settling rapidly form large aggregates or rouleaux, a fact emphasized by Fahraeus, Ponder and others, while in slowly settling blood the ability of erythrocytes to form aggregates is slight (Figs. 1 and 2). A reasonable relationship can be established between the degree of rouleaux formation or size of aggregate and the rapidity of sedimentation in blood with intermediate settling (Experiments I to XVI, incl.).

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* Presented before the Section on Medicine of the College of Physicians of Philadelphia, October 25, 1937.

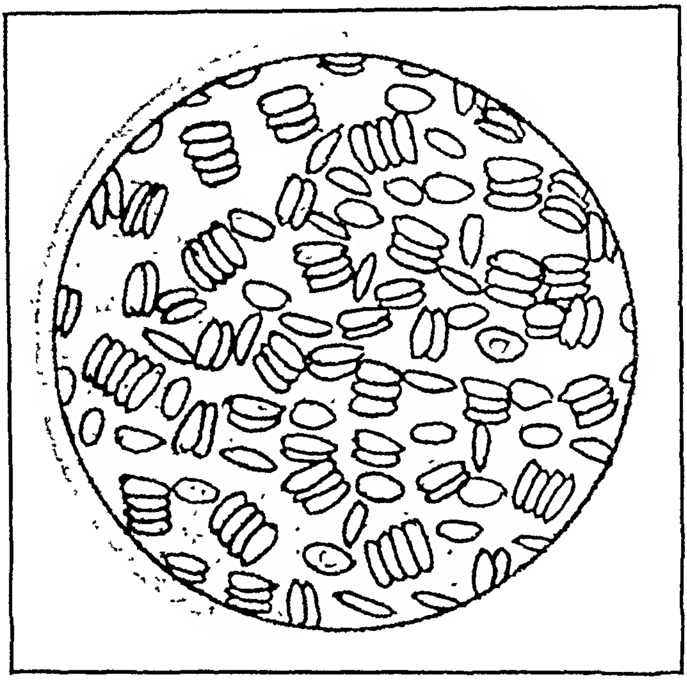

FIG. 1.—Rouleaux formation in slowly sedimenting blood.

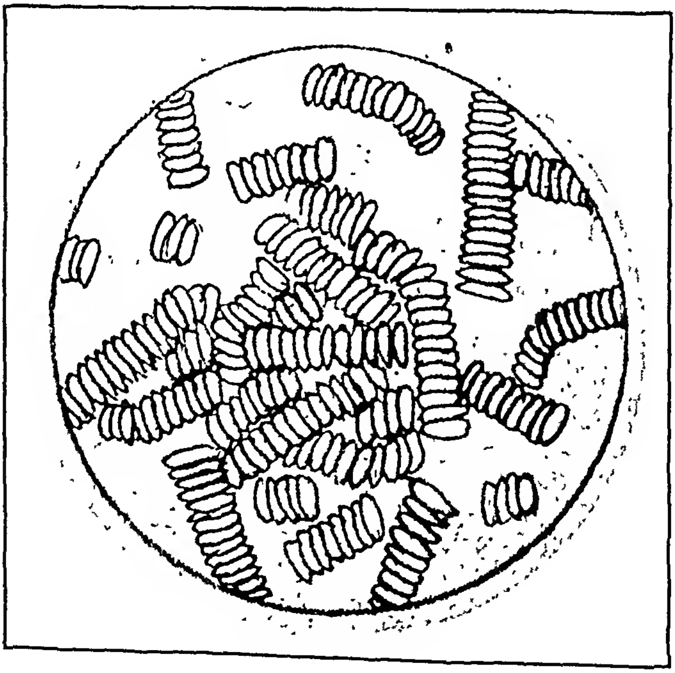

FIG. 2.—Rouleaux formation in rapidly sedimenting blood.

Experiment I. *Interchange of Cells and Plasma.* When cells of slowly sedimenting blood (Fig. 3, *a*) are transferred to plasma of rapidly settling blood (Fig. 3, *b*) they settle rapidly (Fig. 3,*c*); whereas, when cells of rapidly sedimenting blood (Fig. 3 *b*) are transferred to plasma of slowly sedimenting blood (Fig. 3*a*) they settle slowly (Fig. 3 *d*). The number of cells and hematocrit findings, indicated in Figure 3 as volume percentage, are approximately the same in the transferred sample as in the original blood.

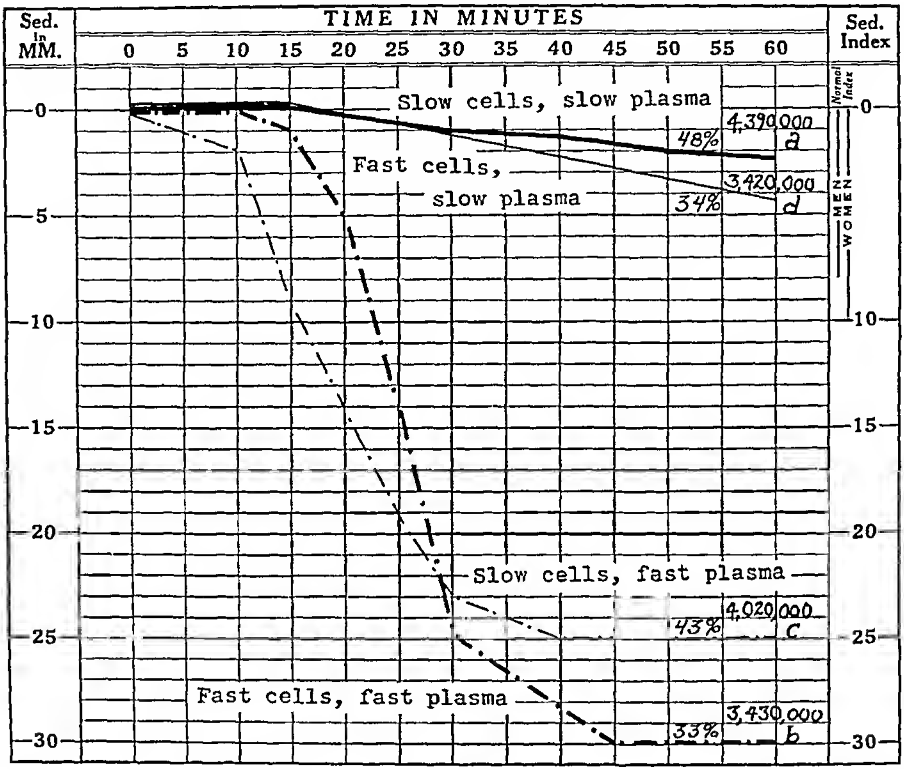

FIG. 3.—Experiment I. Interchange of cells and plasma.

The following table lists the average and the maximum number of cells per rouleaux, and the percentage of cells engaged in rouleaux formation under the different conditions of the experiment.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux* formation.
Graph A (slow cells, slow plasma)	2	2	5
Graph D (fast cells, slow plasma) . .	2	2	5
Graph C (slow cells, fast plasma) . .	20	55	97
Graph B (fast cells, fast plasma)	25	45	90

* With occasional exceptions, all rouleaux studies were made by adding equal parts of saline to the blood and placing this mixture on a glass slide with a cover slip. This procedure uniformly diminished rouleaux formation to a range that facilitated the visual differentiation of the tendency to rouleaux formation of any sample of blood. It was found by trial and error that 50% of saline and 50% of blood was just about the optimum proportion. With a lesser percentage of saline, all bloods form large rouleaux, and are distinguished from one another only with difficulty. On the other hand, if too high a percentage of saline is used, the tendency of all bloods to form rouleaux is very materially diminished or lost.

Experiment II. *Erythrocytes of rapidly sedimenting blood suspended in physiologic salt solution and resuspended in plasma of the original blood.* When the plasma of rapidly settling blood (Fig. 4 *a*) is replaced with physiologic salt solution, there is a progressive slowing in the settling of the red cells (Fig. 4 *b*) until sedimentation is almost inhibited with a dilution of four parts of saline to one part of "fast" plasma of rapidly settling blood (Fig. 4 *c*). When resuspended in the original fast plasma the cells again sediment fast (Fig. 4 *d*).

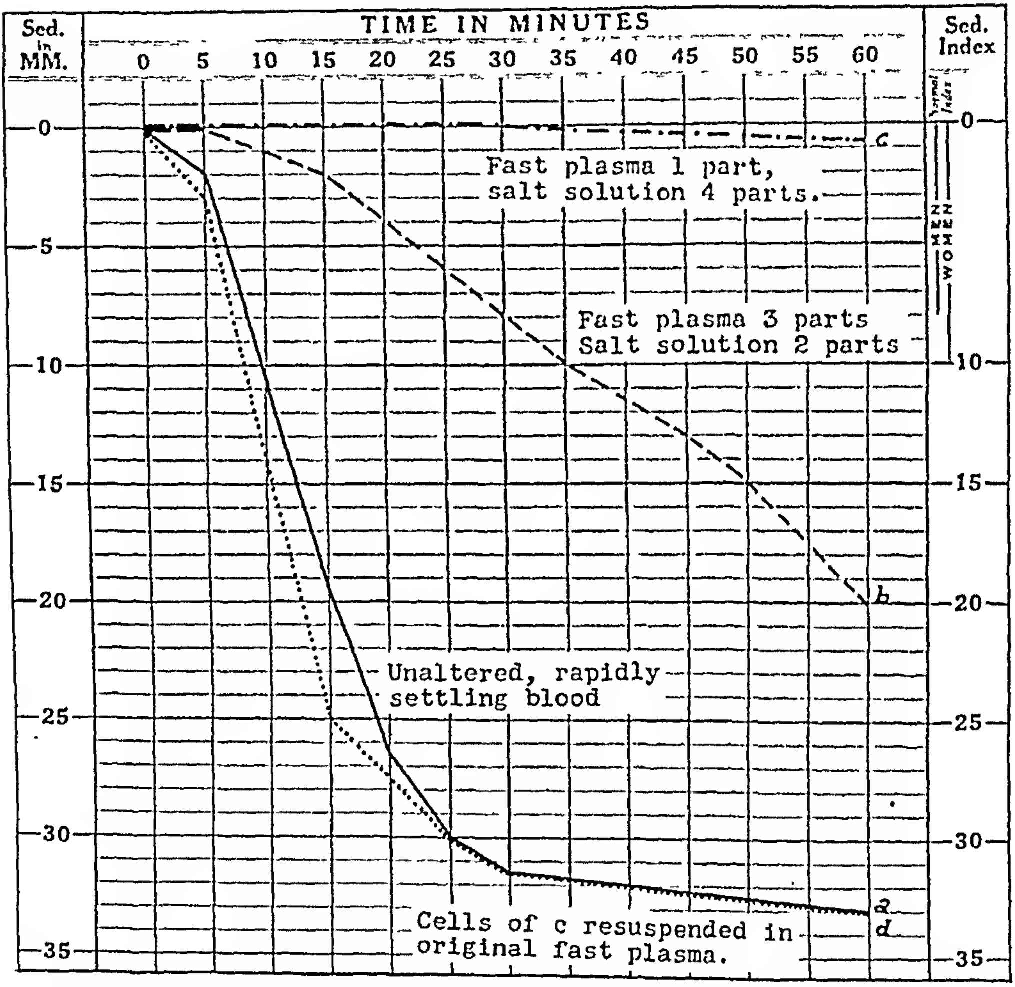

FIG. 4.—Experiment II. Addition of physiologic salt solution to rapidly settling blood.

As in the previous experiment, the difference in behavior of the red cells lies in their ability to form aggregates. In plasma diluted with saline, they fail to form rouleaux. In "fast" plasma they form rouleaux readily. The number of cells in suspension remained the same throughout the experiment. Other details are omitted to conserve space.

Experiment III. *Red cells of rapidly sedimenting blood suspended in Ringer's solution and then resuspended in "fast plasma."* Results with Ringer's solution are identical with those obtained in physiologic salt solution.

Experiment IV. *Addition of lecithin to rapidly settling blood.* When lecithin (1 mg. to 1 cc. of blood) was added to rapidly sedimenting blood, the red cells which previously settled rapidly (Fig. 5 *a*) failed to sediment but remained in suspension indefinitely (Fig. 5 *b*). When the lecithin-treated cells were carefully washed with saline and resuspended in "fast" plasma they again settled rapidly (Fig. 5 *c*).

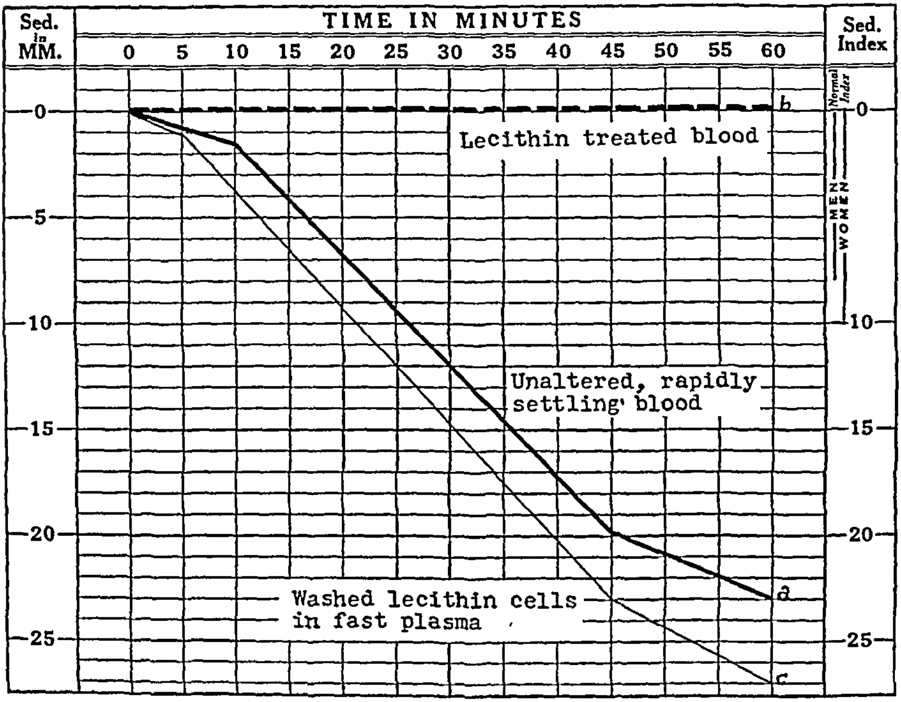

FIG. 5.—Experiment IV. Addition of lecithin to fast settling blood.

In the presence of lecithin the cells failed to form rouleaux, but regained that power in "fast" plasma. An interesting observation in the lecithin-treated cells was the inflated appearance of the red cells, even after repeated washing with saline. The aggregates of the latter consisted of fewer cells, but each aggregate appeared to weigh approximately the same as the aggregates with more cells of the original sample of rapidly settling blood, hence the rate of sedimentation was approximately the same. The percentage of cells engaged in rouleaux formation was the same in both samples of blood. This observation furnishes additional support to the statement that the rapidity of settling is independent of the size or shape of the individual cell, but depends on the total *mass* of the formed aggregate.

The following table lists the average and the maximum number of cells per aggregate and the percentage of cells engaged in rouleaux formation.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, fast settling blood) .	20	40	90
Graph B (lecithin treated blood) . .	No rouleaux formation		
Graph C (washed lecithin cells in fast plasma)	5	22	85

Experiments V, VI, and VII. *Addition of sodium oleate, bile salts or formaldehyde.* When sodium oleate, bile salts or formaldehyde was added to rapidly settling blood, sedimentation was practically inhibited and results were identical with those obtained with lecithin.

Experiment VIII. *Addition of acacia to slowly settling blood.* When acacia was added to slowly settling blood, the erythrocytes which previously settled slowly (Fig. 6 *a*) then settled rapidly. As more acacia was added the rate of settling was increased proportionately (Fig. 6 *b*, acacia, 1 part; blood, 9 parts; Fig. 6 *c*, acacia, 1 part; blood, 4 parts). When the acacia-treated cells were washed in saline and resuspended in "slow" plasma they again sedimented slowly, although not as slowly as the unaltered cells (Fig. 6 *d* and *e*). The rapidity of settling of red cells is intimately bound up with their ability to form rouleaux.

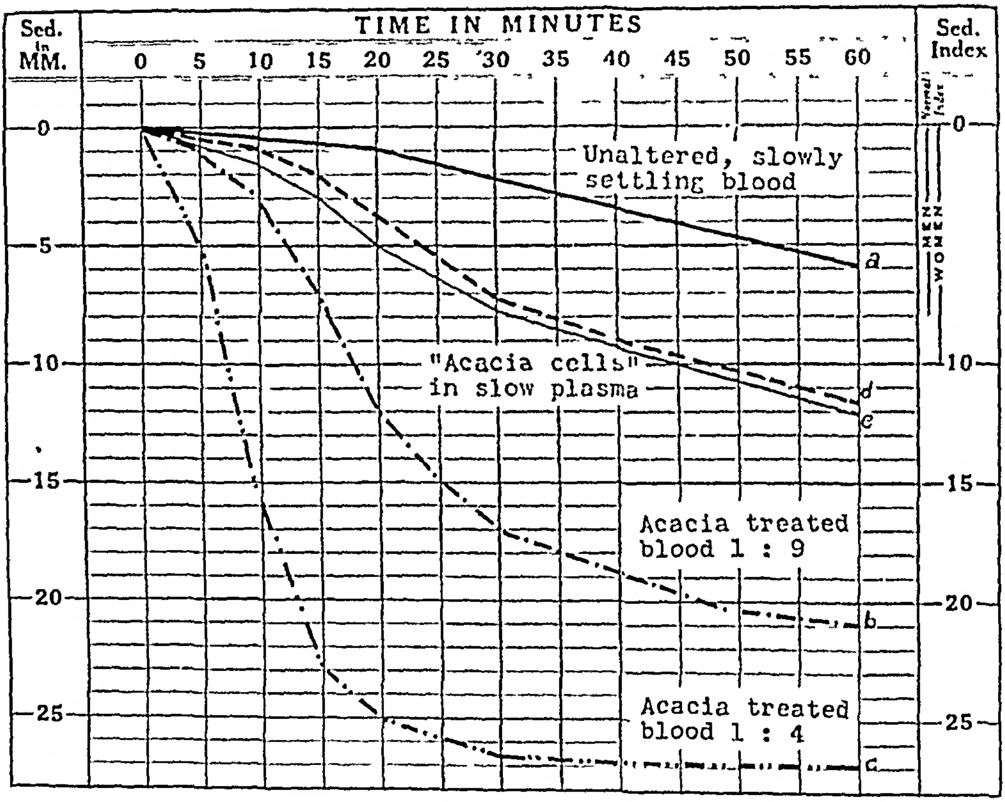

FIG. 6.—Experiment VIII. Addition of acacia to slowly settling blood.

The following table lists the average and the maximum number of cells per rouleaux, and the percentage of the cells engaged in rouleaux formation under the different conditions of experiment.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, slow settling blood)	2	3	5
Graph B (acacia-treated blood 1 9)	15	40	70
Graph C (acacia-treated blood 1 4)	30	90	95
Graph D (acacia cells in slow plasma)	3	6	30
Graph E (acacia cells in slow plasma)	3	6	30

Experiments IX, X, and XI. *Addition of agar, casein or gelatin to slowly settling blood.* When one of the above hydrocolloids was added to slowly settling blood, sedimentation was increased and the results were similar to those obtained with acacia.

Experiments XII and XIII. *Sedimentation in defibrinated blood and in plasma after heat coagulation.* Sedimentation of red cells continued fast in defibrinated plasma of rapidly settling blood (Fig. 7 *c*) and in the plasma of rapidly settling blood from which fibrinogen had been removed by heat coagulation (Fig. 7 *b*). The tendency to rouleaux formation was only slightly interfered with. Figure 7*a* is the unaltered fast-settling blood.

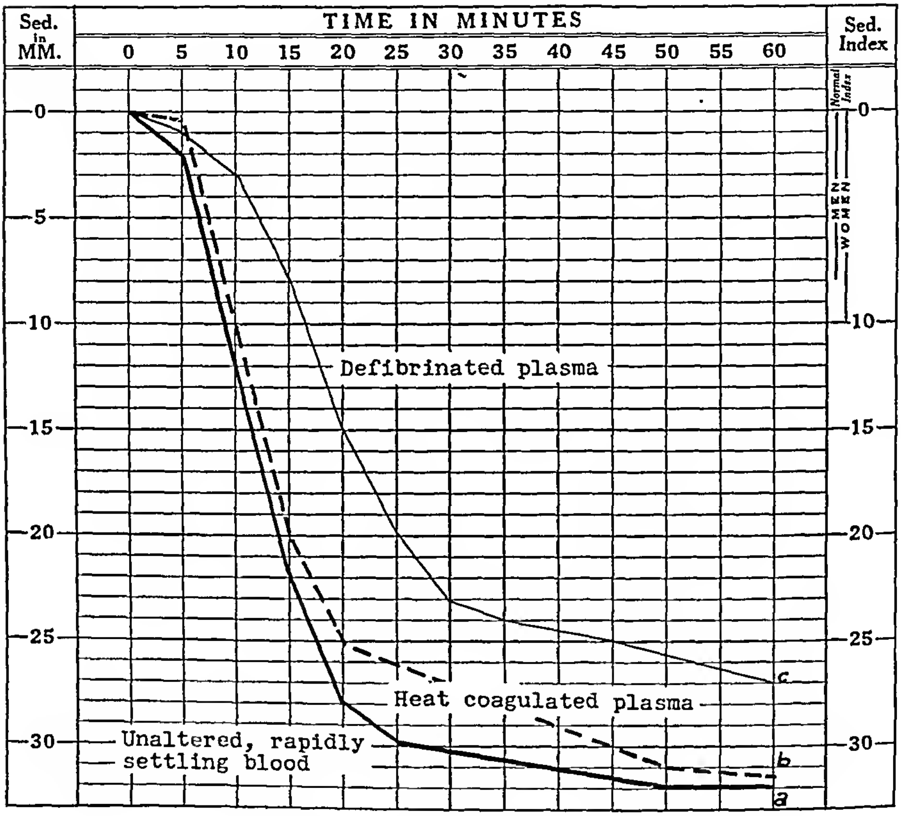

FIG. 7.—Experiments XII and XIII. Sedimentation in defibrinated blood and in plasma after heat coagulation.

The following table lists the average number and the maximum number of cells per aggregate, and the percentage of cells engaged in rouleaux formation.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, fast settling blood) .	25	60	98
Graph B (heat coagulated plasma) . .	25	60	98
Graph C (defibrinated plasma)	15	40	85

Experiment XIV. *Influence of time on rapidity of blood sedimentation.* It is well known that the sedimentation phenomenon disappears with time when blood is permitted to stand at room temperature. Cells which previously settled rapidly will in time refuse to settle. When the red cells which did not sediment were resuspended in fast plasma, they again settled rapidly. Rapidity of sedimentation was once again intimately bound up with rouleaux formation. Details are omitted to conserve space.

Experiment XV. *Relationship of rouleaux formation to sedimentation velocity and of rouleaux formation to red cell count.* Blood sedimentation determinations were made on 104 individuals, for the most part unselected hospital patients. The sedimentation velocity (drop in millimeters per unit of time) was determined for each blood sample by noting on the sedimentation graph the highest number of millimeter drop in any 5-minute interval during the first hour and expressing the result in millimeters.

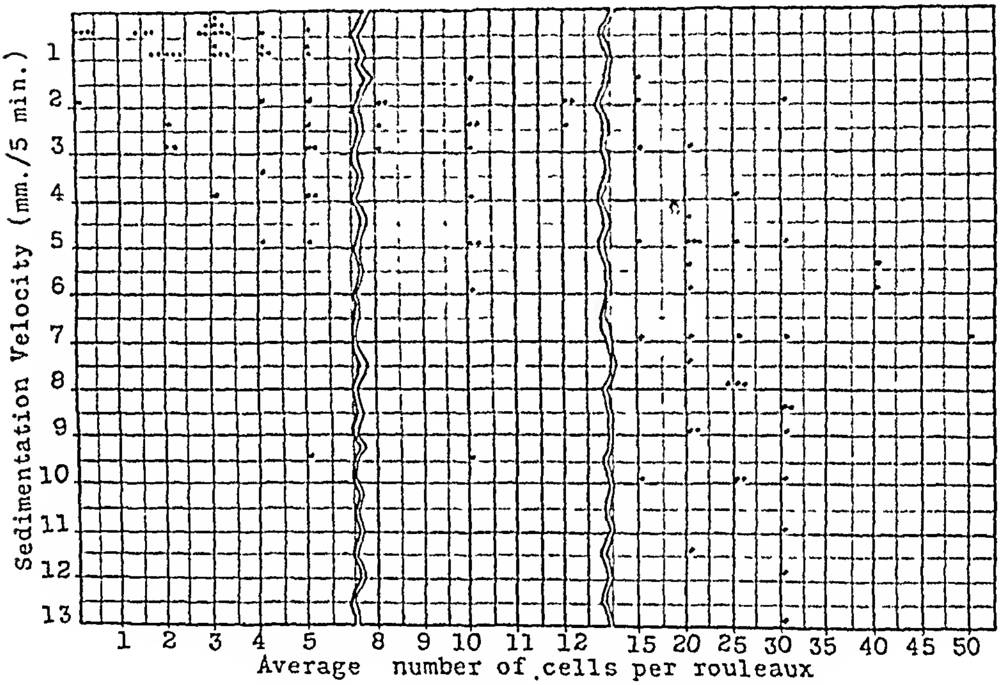

FIG. 8.—Experiment XV. Sedimentation velocity and size of rouleaux.

Rouleaux formation was studied carefully in each patient. Three determinations were made: (1) the average number of cells per aggregate; (2) the highest number of cells per aggregate; and (3) the percentage of cells engaged in rouleaux formation. Red cell counts were made on 91 of the 104 blood samples. The sedimentation velocity, or the maximum number of millimeters the upper level of the sedimenting column of red cells settled in any 5-minute period during the first hour, was plotted against the average number of cells per rouleaux and the corresponding red cell count, and graphs were constructed.

The graph in Figure 8 indicates a close parallelism between sedimentation velocity and the tendency to rouleaux formation. There are few discrepancies at either extreme and these, in part at least, can be explained on technical grounds. Slow sedimentation is invariably associated with small size aggregates and *vice versa.* It is fair to assume that the parallelism would be more striking had a less crude method been used for determining the mass of the aggregate than that of counting the number of cells per aggregate in a few microscopic fields. From the experiment with lecithin (Experiment IV) we are convinced that the size of the red cells is a determining factor in making up the mass of the aggregate, and the larger the cells the fewer the cells per aggregate and *vice versa*. It is also apparent that the procedure of diluting the sample of blood with saline to facilitate the study of aggregation has inherent objections and limitations and involves considerable of a personal equation.

When sedimentation velocity is compared with the red cell count, the relationship is not nearly as close (Fig. 9). Although faster sedimentation velocities are more apt to be accompanied with anemia, it must be remembered that in the cases where sedimentation is rapid, there is usually an associated secondary anemia, the result of the underlying disease, such as advanced cancer, independent of alterations in the suspension stability of the blood.

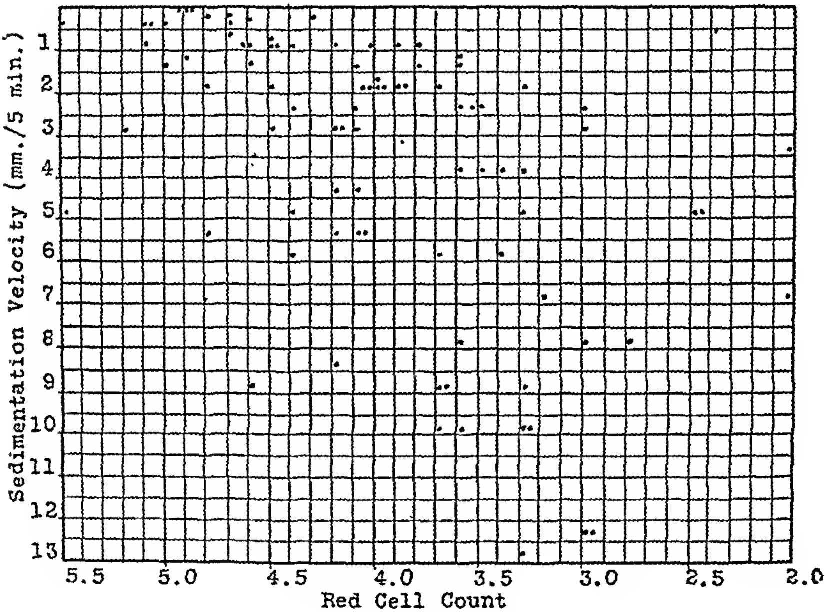

FIG. 9.—Experiment XV. Sedimentation velocity and red cell count.

It is certainly true that sedimentation velocity can be slow or fast and the cell count remain practically the same. Thus a sedimentation velocity of 1 mm. per 5 minutes can be obtained with a red cell count of 5,500,000 as well as with a count of 2,400,000 or any intermediate figure.

Blood Sedimentation and Stokes' Law of Hydrodynamics. The observation that it is the size of the aggregate and not the number of unengaged cells in suspension that is responsible for rapid sedimentation, fits in more or less with Stokes' law of hydrodynamics, which is concerned with sphericle particles held in suspension in a fluid of less specific gravity than the particle itself. According to this law, the rate of settling is proportional to the difference between the specific gravity of the particle and that of the fluid, inversely proportional to the viscosity of the fluid and directly proportional to the square of the radius of the suspended particles.

Differences between the specific gravity of the red blood cells and that of the plasma are without significance. Nor does the viscosity of the blood have an important bearing. The important factor is the size of the particle in suspension.

In this instance, the size of the particle does not refer to the individual cell, but to the size of the *aggregate*. The larger the aggregate, the more rapid the settling and *vice versa*. The establishment of this fact explains such an apparent paradox as increased sedimentation and increased blood viscosity when the reverse would be expected to hold true; and slow sedimentation in the presence of anemia. The individual red cell, regardless of its size or shape or hemoglobin content, has so little mass and the resistance it must overcome is so considerable that it sediments very slowly. On the other hand, when aggregates are formed, the mass of the individual aggregates becomes sufficiently great that they more easily overcome the viscosity of the plasma and settle rapidly. This explains the little increase in sedimentation found in the presence of marked anemia provided there is no associated pathologic condition which in itself may produce rapid sedimentation.

The Three Phases of Blood Sedimentation. We are now in a position to study in detail blood sedimentation as recorded in the form of graphs. Cutler has recognized four distinct graphs, a horizontal line, a diagonal line, a diagonal curve and a vertical curve. The horizontal line is normal and denotes slow sedimentation. The other graphs are abnormal findings and indicate various degrees of increased sedimentation. The vertical curve which indicates the most rapid form of sedimentation, consists of three phases. The first is a slow phase, during which the cells are grouping themselves and forming aggregates. This aggregation period usually varies from 5 to 15 minutes, occasionally as long as 30 minutes. Once formed, the aggregates fall uniformly, more or less in accordance with Stokes' law. This is the second or settling phase and gives rise to the sedimentation phenomenon.

The aggregates settle at their respective speeds indefinitely, depending on the length of the tube until they reach bottom. The aggregates that follow pack on top and the packing stage, or third phase, of sedimentation sets in. This phase is always slow. When all aggregates have settled tightly, sedimentation comes to a standstill.

It is apparent that by the time packing ensues, the sedimentation phenomenon has already taken place and that the packing of cells represents only a rough hematocrit finding, recording the space in the tube occupied by the cells. The packing stage is the only phase of sedimentation that is materially influenced by the degree of anemia. The fewer the cells, the less volume they occupy.

The three phases, aggregation, sedimentation and packing are found in all graphs, in the horizontal normal as well as in the definitely abnormal vertical curve. The difference is in the time required to complete the second stage, or stage of sedimentation which depends on the mass of the aggregates formed during the first or aggregation phase, which in turn is a function of the plasma.

To study the sedimentation phenomenon, one should be concerned principally with the second phase, or phase of settling. The common practice has been, however, to determine the distance the cells have settled at the end of an arbitrary time interval, such as 1 hour, and to express this as the blood sedimentation rate. When sedimentation is rapid and the packing phase has been reached in less than 1 hour, the finding at the end of an hour must reflect not only the sedimentation velocity of the aggregates, but also cell volume, and hence be influenced by the degree of anemia present.

The complete sedimentation graph is therefore seen to reflect two things, blood sedimentation and anemia. The two, however, occupy different positions on the graph and are readily distinguishable. The first two phases of the graph represent the grouping of erythrocytes into aggregates and their sedimentation and are the result of factors within the plasma. The number, size, or shape of cells has little to do with either phenomenon. On the other hand, the third or packing phase records cell volume and is necessarily influenced by such factors as size, shape and number of cells.

The Fallacy of Correcting for Anemia. It is the obvious reflection of the anemia in the packing phase and in the sedimentation index, when sedimentation is rapid and complete within the hour, that has led to efforts to correct for anemia. The proponents for correction for anemia point out, and rightly so, that whenever cell volume is normal, the sedimentation index, that is, the total drop at the end of 1 hour expressed in millimeters, is less than when anemia is present. The decreased sedimentation index after correction, would in their opinion represent blood sedimentation with the anemia factor eliminated. The false premise of this supposition is apparent. Volume percentage and blood sedimentation, as previously explained, are two different things and for all practical purposes have little in common. The confusion results from using a single arbitrary reading as a measure of sedimentation velocity at a time when the sedimentation phenomenon is well advanced.

In the course of our study we corrected a considerable number of blood samples for anemia and plotted sedimentation graphs on the uncorrected as well as on the corrected blood. In a number of instances we corrected the same sample both by volume and by cell count. In every case, when plasma was removed, sedimentation became slower and in direct proportion to the quantity of plasma removed. We next studied the effect of the removal of plasma on the size of the red cell aggregate and it soon became apparent that the removal of plasma interfered with the mechanism of rouleaux formation and resulted in smaller aggregates of red cells.

It thus became clear that it was the reduction in the size of the red cell aggregate and not the greater number of cells in suspension, as is commonly believed, that was responsible for the slower sedimentation rate that invariably followed the removal of plasma to correct for anemia.

When a relatively small quantity of plasma was removed, the mechanism of sedimentation was little interfered with. Although sedimentation was slower in the corrected sample, the shape of the graph was not altered. The corrected curve showed the same general characteristics of the uncorrected curve, only at a slower rate.

On the other hand, when a large quantity of plasma was removed, as was the case when anemia was considerable, 3,000,000 or less, the mechanism of aggregation was seriously interfered with and sedimentation became extremely slow even though the patient from whom the blood was taken was quite ill (Fig. 10).

The proponents for correction call this "over-correction," although the blood count of the corrected sample was 5,000,000, as in other corrected blood samples. This observation is not over-correction. It is a deliberate interference with the mechanism of aggregation of red cells to the point where the sedimentation phenomenon practically disappears.

It is impossible to devise a formula for correction for anemia, based on keeping constant the percentage relationship of cell volume or cell count to plasma volume before instituting sedimentation readings, for the simple reason that the factors responsible for the aggregation of red cells, and hence increased sedimentation, which reside in the plasma, are extremely potent and their concentration specific for the different plasmas. It is the variability of the concentration of these factors in the plasma that determines sedimentation rate and not the quantity of plasma or the number of cells in suspension.

It is not surprising, therefore, to find that those laboratories employing "correction" may report from time to time normal sedimentation findings which do not at all check with the clinical state of the patient.

Artificial Anemia and Sedimentation Velocity. Another observation cited as justification for correction is that the rapidity of settling of red cells can be increased in normal and pathologic blood by simply removing cells and producing an artificial anemia. The natural assumption has been that the increased sedimentation results from a simple reduction in the number of cells in suspension.

Experiment XVI clearly shows that this assumption is not justified. When the proportion of plasma is artificially increased by the removal of cells, the activating factors in the plasma responsible for rouleaux formation have a greater opportunity to drive the remaining cells into rouleaux. The aggregates in slowly settling plasma, however, are never large even when the number of red cells are reduced to 1,000,000 or less. This explains the absence of the steepness to the curve so characteristic of rapidly settling blood, the result of disease with or without an associated secondary anemia. No vertical curves appear because there are no large aggregates (Fig. 11).

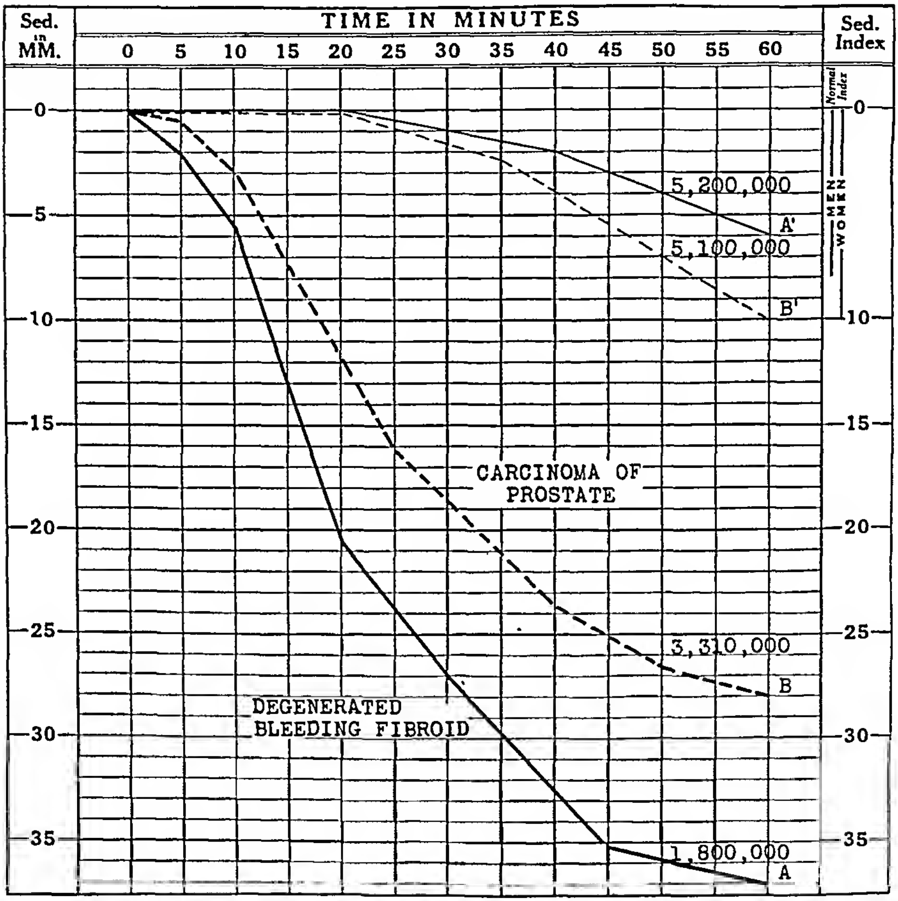

FIG. 10.—Misleading sedimentation rate after "correction."

That the rapid sedimentation is not the result of simply reducing the number of erythrocytes can be further established by suspending the same cells and the same number of cells in physiologic salt solution where there is no tendency to rouleaux formation. Sedimentation becomes extremely slow even though the anemia be marked (Fig. 12).

A dilution experiment, however, fails to make clear the clinical observation that marked anemia, when not associated with a disease which in itself may cause rapid sedimentation, does not result in any significant increase in blood sedimentation. The explanation

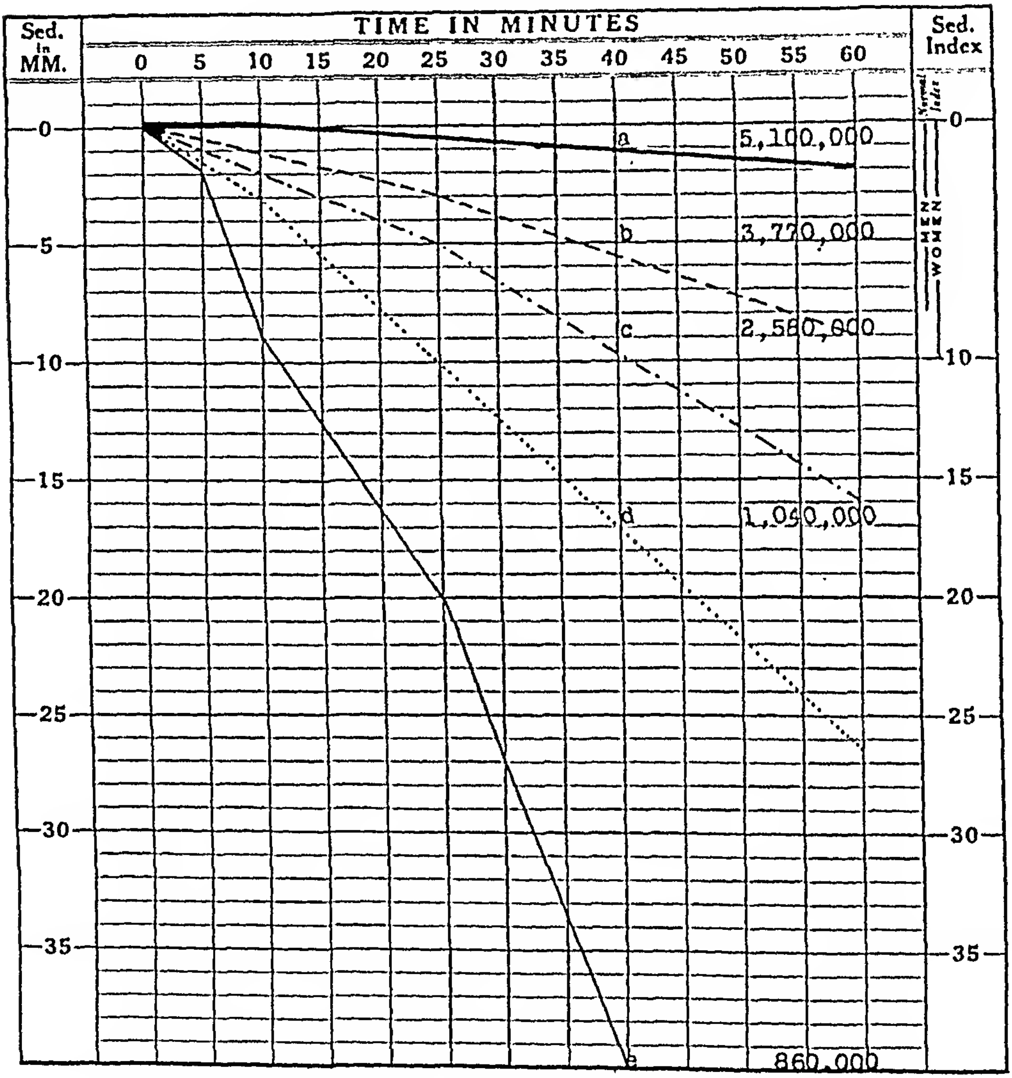

Fig. 11.—Experiment XVI. Artificial anemia and blood sedimentation.

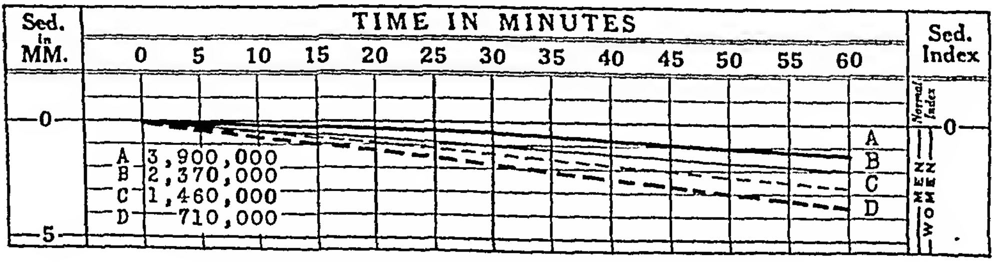

Fig. 12.—Experiment XVI. Artificial anemia in saline.

probably is that the dilution experiment involves large scale manipulations *on a relatively small quantity of blood, a phenomenon* which does not take place during life.

Experiment XVI. *Artificial anemia and blood sedimentation.* The rapidity of blood sedimentation and the red cell counts of 10 healthy individuals were determined. Each blood sample was next diluted by the addition of the patient's own plasma to contain approximately 4, 3, 2, and 1 million red cells per c.mm. and the rapidity of blood sedimentation determined for each dilution.

All graphs were found to be straight lines, no matter how marked the anemia, and the corresponding aggregates to consist of relatively few red cells. The largest aggregates observed were about 18 cells per rouleaux with counts of 1,000,000 or less.

The following table lists the average number of cells, the maximum number of cells and the percentage of cells engaged in rouleaux formation in the case, the sedimentation graphs of which are plotted in Figure 11.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph *a* (5,100,000 r.b.c.)	2	2	25
Graph *b* (3,770,000 r.b.c.)	3	6	25
Graph *c* (2,580,000 r.b.c.)	7	15	50
Graph *d* (1,040,000 r.b.c.)	5	16	75
Graph *e* (860,000 r.b.c.)	5	18	85

No close relationship existed between the degree of artificial anemia and sedimentation index. Each sample of blood appeared to have its own sedimentation characteristics, which it retained throughout the dilution experiment, and graphs with widely divergent sedimentation indices were obtained with practically identical blood counts.

The following table lists the sedimentation index obtained with each of the 10 healthy blood samples, when the red cells in suspension were reduced artificially by the addition of the patient's own plasma to approximate 2,000,000. The sedimentation indices with other dilutions are not recorded, to conserve space.

Case.	Original sedimentation index.	Original blood count in millions.	Artificial anemia (r.b.c. count nearest 2.0 million).	Corresponding sedimentation index.
1	1.5	4.9	2.2	18.5
2	2.0	4.7	2.2	17.0
3	2.0	5.2	1.9	16.0
4	2.0	4.6	2.1	9.0
5	2.5	5.1	2.2	26.0
6	2.5	4.6	2.0	27.5
7	4.2	3.9	2.4	20.5
8	4.5	4.4	2.3	19.5
9	5.5	4.7	2.1	33.0
10	9.5	4.6	2.4	25.0

When the red cells were separated from their plasma medium and resuspended in saline of equal percentage volume and sedimentation graphs constructed, sedimentation was always slow and the graph always a horizontal line, regardless of the number of cells in suspension (Fig. 12). The ability of the red cells to form aggregates was completely lost and microscopically the cells appeared as well formed disks entirely unengaged.

Clinical Observations. Further proof that anemia plays a minor rôle in the rapidity of blood sedimentation is found in the following clinical observations.

A. When pronounced anemia is associated with a disease which in itself is not distinguished by an increased sedimentation rate, such as sickle-cell anemia or bleeding duodenal ulcer, sedimentation of erythrocytes is always slow. Figure 13 *b*, *c*, illustrates sedimentation graphs in sickle-cell anemia and in bleeding duodenal ulcer with anemia of 2,500,000 and 1,360,000 respectively. In spite of the decided anemia, sedimentation is increased little beyond normal.

B. When severe anemia is associated with a disease which in itself may produce a moderate increase in sedimentation, the sedimentation index will be high depending on the degree of anemia present, but the graph will have only a slight curve. A good example is bleeding fibromyoma of the uterus which has undergone mild degeneration (Fig. 13*k*). Anemia in which the counts are higher than 3,500,000 are without appreciable significance.

C. When marked anemia is associated with a disease which in itself may produce rapid sedimentation, such as advanced, ulcerating cancer, the sedimentation index will be high, but there will also be an unquestioned steepness to the graph (Fig. 13, Graph *l*). The steepness of the graph reflects disease; the index portrays anemia as well.

It is obvious from a study of Figure 13*a*, which portrays sedimentation graphs obtained in various clinical conditions, a list of which follows, that the concentration of red cells may vary greatly for the same type of curve and for the same sedimentation index.

Blood sedimentation and anemia are independent phenomena and have little in common.

Conclusions. The present study is a critical appraisal of the scientific basis for the theory that anemia plays an important rôle in the sedimentation of erythrocytes. Consequently, the justification for current efforts to correct for anemia is considered. Our study leads us to the following conclusions:

1. Anemia has little to do with the phenomenon of blood sedimentation. Rapid settling is the result of the red cells forming large aggregates or rouleaux. If no aggregation takes place, sedimentation is slow no matter how marked the anemia.

2. The ability of the red cells to form aggregates is a function of the plasma and is specific for that plasma. The specificity is little influenced by the size, shape or number of cells in suspension.

3. Once aggregates form, they settle at a given rate of speed more or less in accordance with Stokes' law of hydrodynamics. The greater the mass of the aggregate, the more rapid does settling take place and *vice versa*.

4. The current practice of letting a single determination at the end of an arbitrary time interval, such as 1 hour, express blood

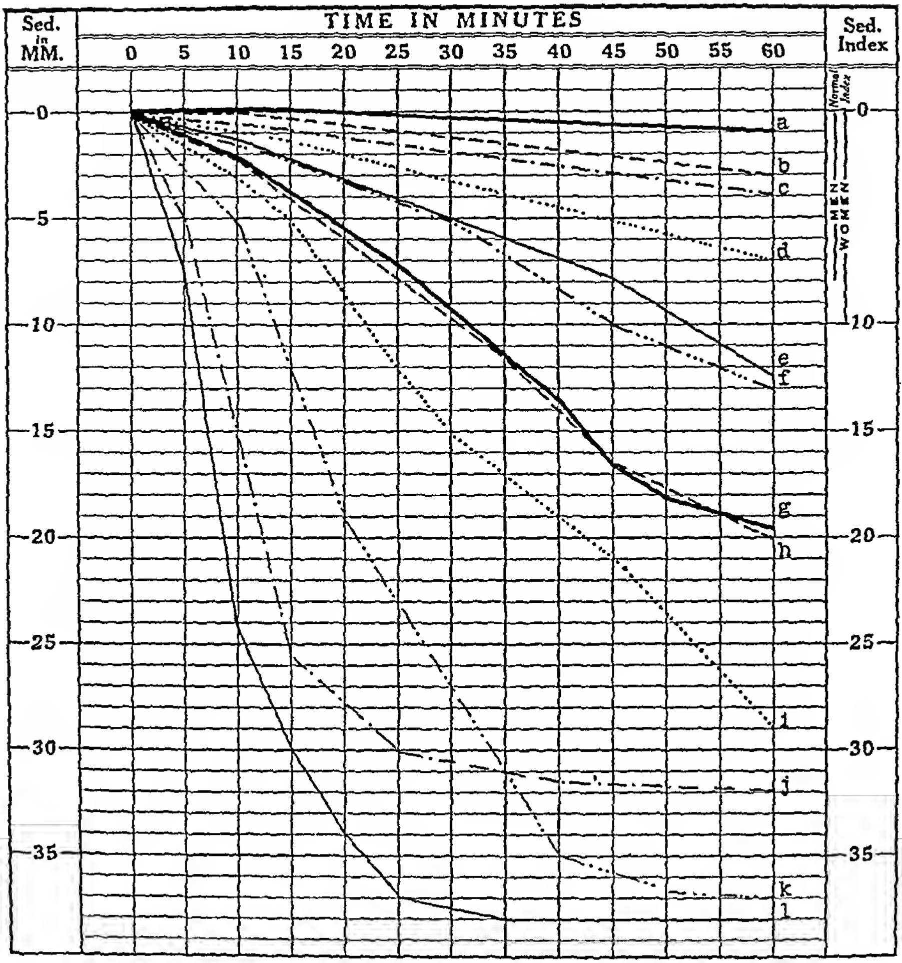

FIG. 13.—Sedimentation graphs and indices in various clinical conditions.

FIG. 13a.—SEDIMENTATION INDEX AND ANEMIA.

	Sedimentation Index.	R.b.c.
a. Healthy male	1	5,100,000
b. Sickle-cell anemia	2	2,550,000
c. Secondary anemia	3	3,860,000
d. Healthy male	7	4,090,000
e. Bleeding peptic ulcer	12.5	1,360,000
f. Coronary disease	13	3,090,000
g. Primary pernicious anemia	19.5	2,320,000
h. Postoperative (nephropexy)	20	5,220,000
i. Carcinoma of stomach	29	2,180,000
j. Lobar pneumonia	32	4,000,000
k. Degenerated bleeding fibroid	37	1,860,000
l. Carcinoma of lung	38	2,400,000

sedimentation fails to study critically the sedimentation phenomenon and leads to erroneous conclusions.

5. When multiple readings are employed, the nature of the graph isolates the anemia factor (packing phase) from blood sedimentation (aggregation and sedimentation phases). The shape of the curve portrays disease, the index reflects anemia as well.

6. One cannot correct for anemia and still get consistent sedimentation findings. The very removal of plasma in an endeavor to correct for anemia interferes with the mechanism of rouleaux formation and sedimentation becomes slow in proportion to the amount of plasma removed.

7. When considerable plasma is removed, the laboratory may report normal sedimentation findings which do not check at all with the clinical state of the patient, a phenomenon referred to in the literature as "over-correction."

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NORMAL VENOUS PRESSURE AS DETERMINED BY A DIRECT METHOD.

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Normal values for venous pressure as given in the literature cover the wide range of 30 mm. to 150 mm. of water. Bedford and Wright,[1] for instance, have quoted figures for the limits of normal determined by direct methods as follows: Castellotti 40 to 70 mm. of water, Corradi 80 to 130, Villaret 120 to 130, Gazzotti 130 to 140. Evans[4] has collected the following figures for the upper limits of normal, also obtained by direct methods: Schott 130 mm. of water, Moog and Ehrmann 100, Arnoldi 103, Fuchs 125, Blumgart 100, Taylor 100, Von Gonezy 120, Ernst and Stagelschmidt 120. Since all the above determinations were made on "normal subjects," it is probable that the differences obtained resulted from differences in technique.

Further data from the literature may be tabulated as follows:

Author.	Date.	Direct method.	Subjects studied.	Venous pressures.	
				Extremes.	Average.
Bedford and Wright[1] .	1924	Claude	34 medical students	90% were between 50–150 mm. of water	Not given
Evans[4b]	1932	His own	Miscellaneous group having various diseases	75–175 mm. of water Majority between 100–150	Not given
Leaman[8]	1935	Evans	Normal group	40–120 mm. of water	Not given
Wartman[10]	1935	Griffith, Chamberlain, and Kitchell	31 normal persons	60–120 mm. of saline	83 mm.
Harrison[7]	1936	Moritz and Tabora	20 normal persons	30–75 mm. of saline	54 mm.
Berger[2]	1937	Moritz and Tabora	20 normal persons	Not given	77 mm. of 5% sodium citrate solution
Gibson and Evans[5] .	1937	Evans[4a]	90 normal persons	50–120 mm. of water	80 mm.

Moritz and Tabora[9] described their direct method in 1910. Accurate details of the position of the subject's shoulders and arm were given, and photographs of their apparatus in use were included. They studied 29 "normal subjects," obtaining an average venous pressure reading of 52 mm. of physiologic saline, with the majority falling between 40 to 80 mm.

In 1934, Griffith, Chamberlain, and Kitchell presented their modification of the method of Moritz and Tabora. Besides a marked simplification of the apparatus, these workers also changed the technique of its use. Thus instead of maintaining the arm in right angle abduction at the shoulder, with slight flexion at the elbow, and with the hand in half pronation, they prescribed that the "arm and forearm (be) extended by the side in supination." From 250 readings on normal subjects they gave an average range of from 80 to 110 mm. of physiologic saline, with a normal range of 60 to 120 mm.

The purposes of the study presented below were to discover, if possible, an explanation for the difference between the figures of Moritz and Tabora and those of Griffith, Chamberlain, and Kitchell; to establish a standard technique for the method of the latter; and to determine thereby normal venous pressure values.

Method. The apparatus was constructed according to the specifications of Griffith, *et al.* The theory of its use may be stated briefly. By means of a level fitted with accurately measured legs and clamps for a glass tube, the zero point of a manometer can be held at the level of the right auricle. A saline column in the manometer is carried into a vein of the subject's arm by means of rubber tubing, a Kaufman-Luer side arm syringe and an intravenous needle. Within certain limits, the system thereby created may be considered a direct tube-and-fluid connection between the venous entrance to the right auricle and the manometer. Thus any pressure effect at the former will be reflected at the latter.

Table 1.—Venous Blood Pressure in Normal Subjects (Griffith Position).

Case.	Age.	Sex.	Venous pressure (mm. of saline). Right arm.	Venous pressure (mm. of saline). Left arm.	Average.
1	23	F	85	95	
			120	120	
			105	105	105
2	22	F	...	100	
			115	135	
			120	120	118
3	25	M	110	(150)	
			105	(140)	
			(140)	(180)	
			115	115	111
4	23	M	130		
			125		
			125	130	127
5	28	M	130		
			110	...	120
6	23	M	100		
			130	125	
			95	105	111
7	23	M	95		
			85		
			105	105	
			60	60	85
8	24	M	75		
			90		
			90	105	90
9	24	M	(150)	100	
			105	105	
			115		
			115	95	106
10	25	F	80		
			100	...	90
11	23	M	140	140	140
12	22	M	130	110	120
13	32	F	110	110	110
14	23	M	(180)		
			(175)		
			(145)	(130)	
			(180)	(140)	
15	24	M	(180)		
			(190)		
			(255)	(125)	

The first series of tests were made on a group of 14 medical students and one nurse, all of whom were perfectly healthy. The Griffith technique was used, including the feature of extending the arm and forearm by the side in supination. The results of these tests are given in Table 1. An average of 4 determinations was obtained on each subject.

Of the 65 readings recorded, the 15 appearing in parentheses were thought to be inaccurate either because they failed to agree with other readings made on the same subject, as in Case 9, or because the behavior of the fluid level during the experiment was such that no definite value could be assigned. At times the fall in the saline column after removing the reservoir was unduly slow, or perhaps when a level seemed accurately attained, a moderate inhalation would reduce it by 20 to 30 mm. to a new level. Occasionally paradoxical respiratory fluctuations were encountered in which the venous pressure rose with inspiration and fell with expiration. Under these various circumstances, the readings were considered without value.

Among the 50 supposedly reliable determinations, there were high and low extremes of 140 mm. and 60 mm. of physiologic saline solution. The average value for venous pressure of the first 13 cases was 110 mm. The results obtained on the next 2 cases (14 and 15) were not only far higher but were also poorly defined. Furthermore, the average of 110 mm. was known to be twice as high as the average described by Moritz and Tabora. Therefore, it was suspected that all the readings were unduly high and that the technique was at fault.

TABLE 2.—NORMAL VENOUS BLOOD PRESSURE (MORITZ AND VON TABORA POSITION).

Case.	Age.	Sex.	Venous pressure. (mm. of saline).		Average.
			Right arm.	Left arm.	
14	23	M	75	75	
			90	100	
			75	80	82.5
15	24	M	75	65	70
16	24	M	85	85	
			90	85	86
17	24	M	35	35	
			30	30	32.5
18	24	M	95	95	
			80	80	87.5
19	23	M	85	85	
			85	80	84
20	22	M	95	95	
			75	85	87.5
21	24	M	85	95	
			90	90	90
22	24	M	90	90	
			80	80	85
23	24	M	85	90	
			55	65	
			55	75	71
24	24	M	75	75	
			65	75	72.5
25	25	M	95	90	
			100	95	95
26	29	M	55	55	55
27	22	M	50	50	50
28	22	M	90	85	
			100	95	92.5
29	22	M	70	70	
			65	65	67.5
30	22	M	75	80	
			80	80	79

Cases 14 and 15 were again studied in exactly the same manner excepting that the position of the arm was maintained according to the instructions of Moritz and Tabora. The results were strikingly different. The levels were obtained quickly, and the figures were found to be much lower (see Table 2). During each of these 8 tests, when the end point had been established, the arm was carefully shifted to the position previously used. Invariably the level promptly rose. For instance, in the right arm test of Case 15 the pressure rose within 45 seconds from 75 mm. to 200 mm. Both of these men had particularly large upper arms with firm flesh. Thus the obvious explanation for the phenomena described would seem to be that on adduction of the arm, squeezing of the veins occurred about the shoulder and axilla, thereby raising the venous pressure at the elbow. Similar shifts in position of the arm were studied on 15 other subjects. Without fail adduction caused a rise in pressure; and abduction, a fall. It was observed that the thinner the arm and the flabbier the musculature and fat layers, the less was the pressure excursion. This fact is considered supporting evidence for the above explanation. In view of these findings, all subsequent determinations were done with the test arm in at least 70 degree abduction at the shoulder.

Another possible explanation for venous pressure irregularities attending changes in the position of the test arm was offered in 1931 by Brandt and Katz.[3] They believed that adduction of the arm affected the anatomic relationship between the clavicle, first rib, and subclavian vein in such a way as to exert pressure on the vein. They found that paradoxical respiratory changes and unduly high venous pressures could be abolished by placing the arm in the position advocated by Moritz and Tabora.

The Technique Used in Obtaining the Figures Recorded in Tables 2 and 3. The subject is requested to remove all clothing encircling the upper arms and shoulders or covering the angle of Louis. He then reclines on his back on a perfectly flat, firmly cushioned examining table. A thin pillow under the head is permissible. A blood-pressure cuff is adjusted to the upper arm. The lower arm is supported on a small adjoining table, using folded towels to rest it in the most comfortable position (Fig. 1). This maneuver nearly always brings the antecubital surface to lie close to the horizontal level of the posterior axillary line. The subject lies close enough to the edge of the examining table so that his upper arm is suspended free from any points of contact with either table. He is then instructed to breathe at the rate of about 12 respirations per minute. A metronome has proved useful in this respect. If it is set at 48 strokes per minute, the subject inhales slowly for 2 beats and exhales for 2 beats. Under the above conditions, he rests for 15 minutes.

Meanwhile, the entire apparatus, excepting the wooden leveling device, is sterilized by boiling. When all is assembled, about 12 to 15 cc. of sterile physiologic saline are poured into the reservoir. The fluid is allowed to flow through the system until all bubbles have been eliminated and the stream is seen to flow briskly and evenly. This usually takes about 4 to 5 cc., leaving the 8 to 10 cc. necessary for the test.

When the 15 minutes have passed, the pulse and arterial blood pressure are taken. The antecubital space is then cleansed with alcohol. The cuff is inflated to a pressure half way between the diastolic and systolic readings, and the needle is promptly introduced preferably into the median basilic vein. As the blood enters the syringe, the cuff is quickly deflated and removed from the arm. At the same time, the assistant is raising the manometer and reservoir as high as possible, to insure a maximum head of pressure of the saline column which is allowed to wash the blood out of the syringe into the vein. During the ½ to ¾ minute it takes adequately to clear the syringe, the arm is adjusted comfortably with abduction at the shoulder to approximately a 70-degree angle. The elbow is slightly flexed and the forearm is rested in half pronation (Fig. 1). The position of the needle in the vein may then be altered to insure the fastest flow of saline. This can be determined by observing the falling fluid level in the reservoir.

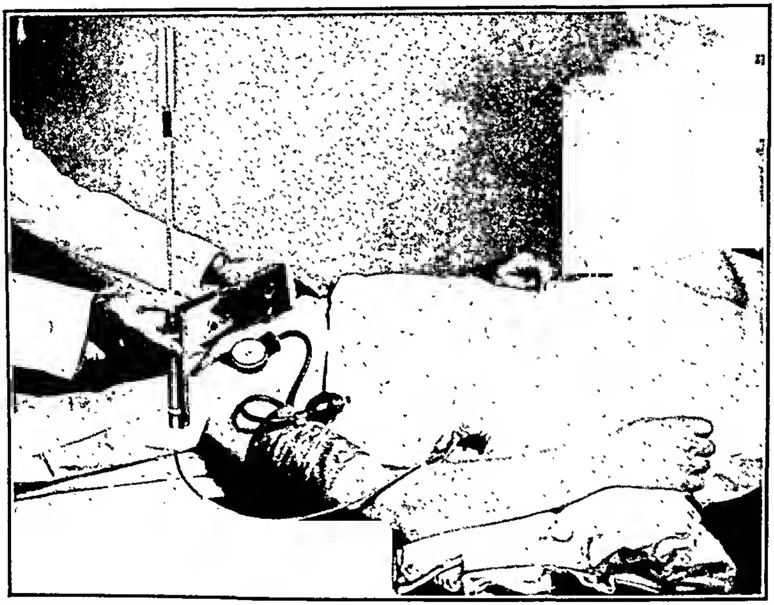

Fig. 1.—The apparatus as described by Griffith, Chamberlain, and Kitchell, and the position of the arm as prescribed by Moritz and Tabora.

When the speed of flow is maximum and the syringe is practically clear, the shorter leg of the level is set at the angle of Louis. The reservoir is removed by simply sliding it off from the manometer. The excess saline is allowed to spill, since any attempt to pinch the rubber connection is apt to introduce a bubble into the manometer.

As the reservoir is detached, the position of the second hand of a watch is noted. The fluid level normally falls in the manometer at the following rate in millimeters per successive 5 seconds:

The first 5 secs.	.	100 mm.
5 secs.	.	50 mm.
5 secs.	.	40 mm.
5 secs.	.	30 mm

The first 5 secs.	.	20 mm.
5 secs.	.	10 mm.
5 secs.	.	5–10 mm.
5 secs.	.	5–10 mm.

As the venous pressure level is approached, the meniscus is often seen to descend in step-like fashion with sharp falls on inspiration and stationary levels or possibly slight rises associated with expiration. When a fixed level has been reached, the time is again noted. If the procedure has taken over 70 to 80 seconds, it is likely that the technique was at fault. Most levels are easily obtained within 40 to 60 seconds.

In order further to check the free flow of saline and blood, the manometer is lowered. A prompt rise in the saline level occurs which recedes more slowly when the manometer holder is again leveled off. If the manometer is then elevated, the fluid level sinks. However, it again returns to the venous pressure point, when the manometer is properly adjusted.

The Valsalva experiment ("bearing down" effect) with its increasing the venous pressure and the taking of a deep breath with its lowering the venous pressure were maneuvers not used in determining the true venous pressure. It was found that too often these experiments gave irregular results, sometimes even establishing new venous pressure levels which would last a number of minutes. In order to avoid any diurnal variation, all determinations were made in the late morning before luncheon. The general principle of maintaining basal conditions and avoiding any artificial redistribution of pressure effects, was rigidly adhered to in this study.

When the test is concluded, the syringe, needle and rubber tubing are carefully rinsed free of any blood. Each day the apparatus is used, the manometer is cleaned with bichromate and sulphuric acid solution. This insures smooth running of the fluid column and obviates bubble formation. Periodically, the correction figure for capillary attraction of the saline in use is obtained according to the method of Griffith, *et al.*

The second series of tests were performed with the revised technique on 17 healthy medical students, all under 30 years. The results are presented in Table 2. An average of 4 determinations was made on each subject. The lowest value obtained was 30 mm. of saline; the highest, 100. The average venous pressure for the group was 76 mm. of saline.

The third group similarly studied was comprised of 18 individuals who were over 30 years and gave no signs or symptoms of heart failure. Their data appear in Table 3. An average of 2 tests was done on each case. The extremes in values obtained were 10 mm. and 95 mm. of saline. The average venous pressure for this series was 54 mm. of saline.

TABLE 3.—VENOUS BLOOD PRESSURE IN PERSONS NOT SUBJECT TO HEART DISEASE.

Case.	Age.	Sex.	Diagnosis.	Blood pressure.	Pulse.	Venous pressure (mm. of saline).		Average.
						Right arm.	Left arm.	
31	32	F	No disease	115/80	76	80	85	
				120/80	72	70	70	76
32	30	M	No disease	110/75	84	70	75	
				110/75	72	70	65	70
33	36	F	No disease	120/80	78	90	85	
				125/85	73	95	95	91
34	58	F	Neurodermatitis	160/90	96	60	60	60
35	55	M	Tonsillitis	125/80	72	50	50	50
36	57	M	?Cirrhosis	135/85	72	45	45	45
37	61	M	Epithelioma	130/85	66	25	40	32.5
38	45	M	Tonsillitis	125/85	60	90	90	90
39	54	F	?Ca. stomach	150/90	96	40	55	47.5
40	48	F	Hemoptysis	125/80	120	75	65	70
41	49	F	?Appendicitis	230/120	72	..	75	75
42	55	F	?G. I. malignancy	125/80	72	45	50	47.5
43	40	F	?Pyelitis	140/100	105	45	45	45
44	54	M	Constipation	95/60	72	30	30	30
45	74	M	Ca. rectum	125/80	96	10	10	10
46	80	M	Pharyngitis	120/80	120	50	75	62 5
47	63	M	Diverticulitis, colon	180/110	72	40	..	40
48	46	M	Thrombophlebitis, both legs	150/80	96	30	30	30

Discussion. Among the 108 venous pressure determinations attempted on the 35 cases shown in Tables 2 and 3, there were only 2 failures, 1 due to faulty introduction of the needle into the vein, the other unexplained. This record stands in marked contrast to the 15 failures among the 65 tests done without proper regard for the position of the subject's arm. That this technical detail is important is further substantiated by the fact that 10 of the 15 irregularities occurred in Cases 14 and 15 who later gave perfectly regular results when their arms were supported as shown in the photograph.

In this position also, a lower range of venous pressure was consistently found for cases in general. Thus, the probable explanation for the differences in normal values described by Moritz and Tabora and Griffith, *et al.* rests on the basis of position of the test arm. The figures in Table 1 fall reasonably well in line with those reported by the Griffith group. The values in Table 2 and especially in Table 3 are entirely comparable with those presented by Moritz and Tabora. It is therefore apparent that similar techniques determine similar results. Hence, since the fundamental technique of Moritz and Tabora has proven the more satisfactory in this investigation, the lower range of normal values is considered the more accurate.

It is interesting to note that the average venous pressure for the 18 cases over 30 years was 54 mm. of saline; and for the 17 cases under 30 years, 76 mm. of saline. For all 35 cases the general average was 65 mm. There was no correlation observed between arterial blood pressure and venous blood pressure. Nor were any significant differences in venous pressure found between the two arms of a given subject.

Summary. 1. Normal venous pressure values obtained by various direct methods are quoted from the literature.

2. Venous pressures of 48 normal subjects determined according to the method of Griffith, Chamberlain, and Kitchel are presented in 3 tables. The first series (Table 1) was studied with the test arm "extended by the side in supination." In the second and third series, the arm was abducted to at least a 70-degree angle and supported approximately as originally described by Moritz and Tabora. It was demonstrated that this single change in a technical detail accounted for greater accuracy in obtaining readings, more consistent results, and a lower range of venous pressure values (Tables 2 and 3).

3. Details of the technique used are given.

4. The normal range of venous pressure thereby obtained in 35 cases was from 10 to 100 mm. of physiologic saline solution, the average value being 65 mm. The older age group tended to have lower levels than the younger.

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THE BODY AS A VOLUME CONDUCTOR AND ITS INFLUENCE ON THE ELECTRICAL FIELD OF THE HEART.

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The assumption that the body is a large, homogeneous conducting medium, forms the basis for much recent work in electrocardiographic analyses. Wilson[8] accepts this fact as conclusive, and

Kossmann[5] in a later publication makes similar deductions. However, the very original methods employed by Smith and Kountz[6] in obtaining an electrocardiogram from a cadaver, connected to an isolated dog heart-lung preparation by means of a shunt, gave evidence that other factors must be considered. Similarly, Katz and Korey[2] deduced from their work that certain tissues conducted impulses better than others, and more recently, Katz, Gutman and Ocko[3,4] reported significant results by altering types of conductors immediately adjacent to the heart.

In the work of Smith and Kountz[6] the gravitating fluids in the body of the cadaver might influence the changes in the records reported by them. The factor of mechanical distortion inherent in the technique employed by Katz and Korey[2] could conceivably explain some of their results. In their later experiments, Katz and his co-workers[3,4] used shunts, the material of which represented such individual variation in the coefficient of conduction, as to find no parallel in the tissues of the body. Thus, there are factors of possible error in the methods pursued by these investigators.

In view of these considerations, we devised a series of experiments to obviate the criticisms mentioned above.

Experimental. The following experiments, examples of repeated procedures, were performed using similar technique throughout. Dogs were used in each instance and one of the Barbiturate compounds intravenously was the anesthetic employed.

Experiment I (Fig. 1). *Shifting the electrode on an extremity produces no appreciable change in the amplitude or the contour of the electrocardiogram.*

The following experiment was performed to prove or disprove this contention:

A. A dog's femoral vein, artery and nerve were isolated. Right arm electrode was inserted in the fourth intercostal space to the left of the sternum. The left arm electrode was inserted in the distal portion of the left leg.

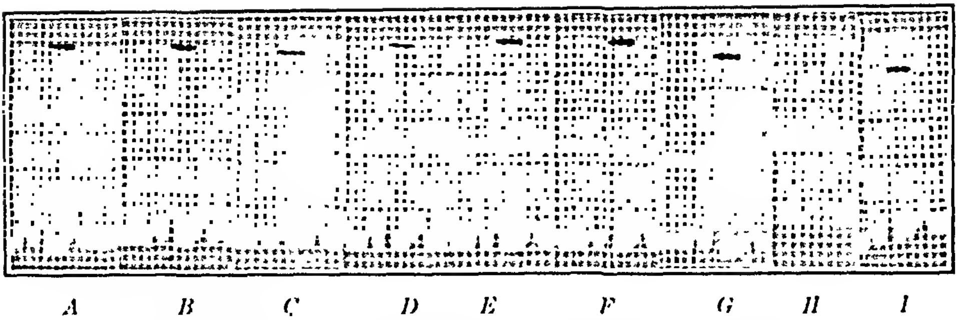
Electrocardiograms were taken after each of the following procedures: (*a*) Control, (*b*) complete circular interruption of the skin in the mid-thigh area, (*c*) ligation of the femoral artery, (*d*) ligation of the femoral vein, (*e*) ligation of the femoral nerve, (*f*) complete severance of the main muscle-mass of thigh, (*g*) periosteum of the femur stripped, (*h*) leg amputated, (*i*) ends of bones brought in apposition.

It will be noted that no appreciable change occurs in the records.

B. The same experiment, severing the structures in reverse order produced comparable results.

Experiment II (Fig. 2). *Altering the contact relationship of lung to chest wall, diaphragm and pericardium.*

Leads I and V (right arm electrode in fourth interspace to the left of sternum; left arm electrode on left leg) were taken as controls. Bilateral, controlled, progressive and simultaneous pneumothorax was performed. Lateral shifting of the heart was thus prevented. Air was introduced into both thoracic spaces simultaneously in quantities from 100 cc. to 600 cc. (Fig. 2).



(The height of the *R* wave is indicated by a horizontal line.)

FIG. 1.—Experiment I. *A*, Control electrocardiogram. *B*, The skin in the mid-thigh area was completely interrupted and an electrocardiogram taken. *C*, The femoral artery was ligated and severed and electrocardiogram taken. *D*, The femoral vein was ligated and severed and electrocardiogram taken. *E*, The femoral nerve was severed and electrocardiogram taken. *F*, The main muscle mass of the thigh was completely severed to the bone in the mid-thigh region and electrocardiogram taken. *G*, The periosteum of the femur was stripped and an electrocardiogram taken. *H*, The bone was completely severed and the amputated leg held away, no electrocardiogram, of course, registered. *I*, The stumps of the bone were brought in apposition and an electrocardiogram taken.

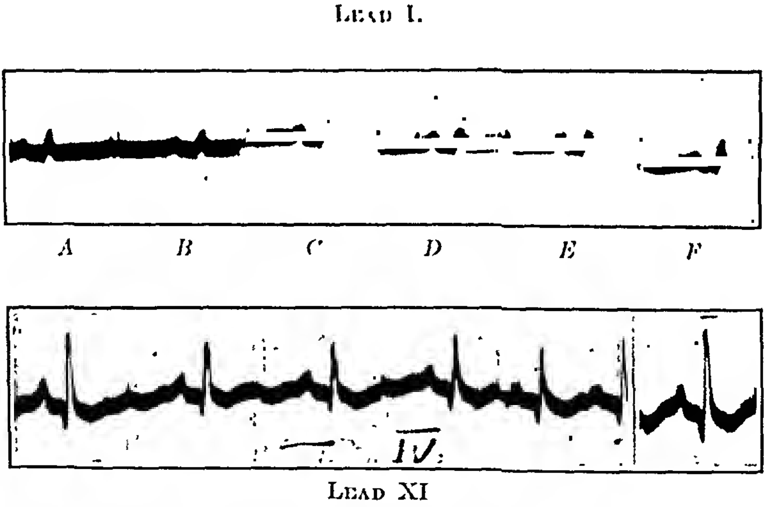


FIG. 2.—Experiment II. *A*, Control electrocardiogram. *B*, Electrocardiogram after 100 cc. of air were equally dispersed into the pleural cavities. *C*, Electrocardiogram after 300 cc. of air were equally dispersed into the pleural cavities. *D*, Electrocardiogram after 500 cc. of air were equally dispersed into the pleural cavities. *E*, Electrocardiogram after 600 cc. of air were equally dispersed into the pleural cavities. *F*, Control electrocardiogram after all the air had been withdrawn from both pleural cavities.

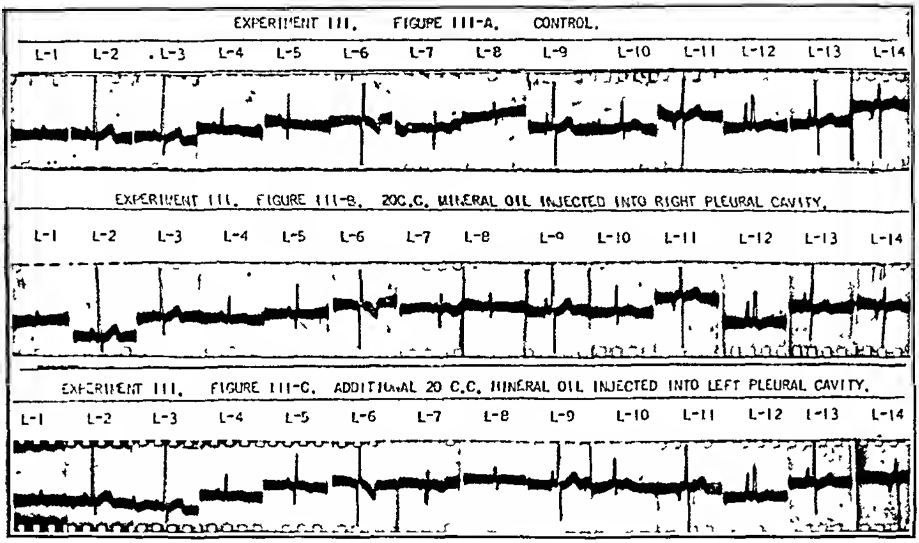

EXPERIMENT III. FIGURE III-A. CONTROL.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14
EXPERIMENT III. FIGURE III-B. 20C.C. MINERAL OIL INJECTED INTO RIGHT PLEURAL CAVITY.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14
EXPERIMENT III. FIGURE III-C. ADDITIONAL 20 C.C. MINERAL OIL INJECTED INTO LEFT PLEURAL CAVITY.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14

Fig. 3.

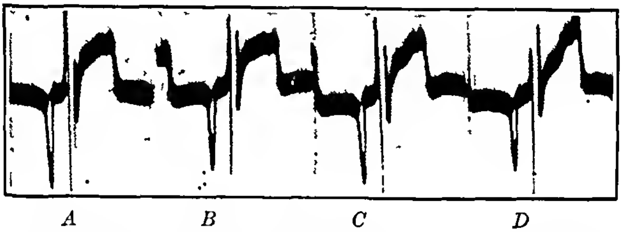


Fig. 4.—Experiment IV. Right arm electrode in middle bronchus of left lung Indifferent electrode in left chest. Left chest opened in fourth intercostal space. Left pleural cavity bathed with mineral oil *A*, Control electrocardiogram. *B*, Electrocardiogram after ligation and severing of left pulmonic veins *C*, Electrocardiogram after ligation and severing of left pulmonic artery. *D*, Electrocardiogram after ligation and severing of a left bronchial artery

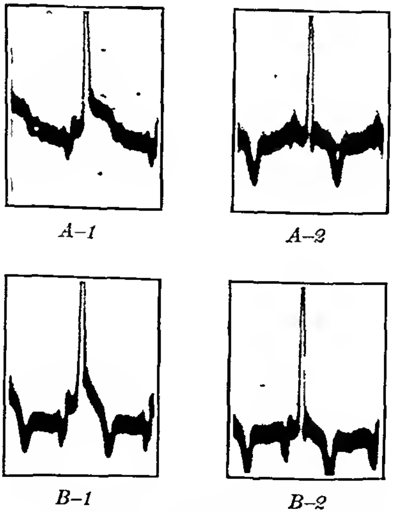
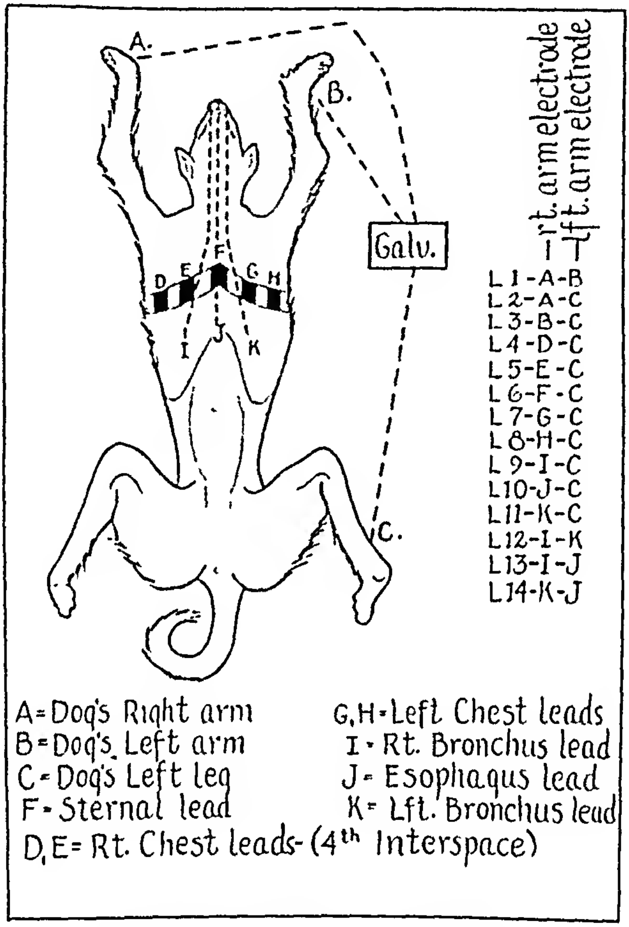


Fig. 5.—Experiment V. Left pulmonary artery ligated and left pulmonary veins isolated and distal and proximal ligatures placed beneath them. *A–1*, Control electrocardiogram with right arm electrode in lower bronchus of left lung and left arm electrode in left leg. *B–1*, Control electrocardiogram with right arm electrode in lower bronchus of left lung 1 cm. removed from that of *A–1* and left arm electrode as in *A–1*. *A–2*, *A–1* repeated after ligation and severing of pulmonary veins. *B–2*, *B–1* repeated after ligation and severing of pulmonary veins.

Noteworthy lessening of voltage in the *QRS* complex, Lead I with increasing intrathoracic pressure is apparent. There is also notching at the apex of this complex. In Lead V there is likewise decrease in voltage of *QRS* wave and notching, which tends to shift from its apex toward the isoelectric line with increase in air pressure.


A.
B.
C.
D
E
F
G
H
I
J
K
Galv.
I rt. arm electrode
I lft. arm electrode
L 1-A-B
L 2-A-C
L 3-B-C
L 4-D-C
L 5-E-C
L 6-F-C
L 7-G-C
L 8-H-C
L 9-I-C
L 10-J-C
L 11-K-C
L 12-I-K
L 13-I-J
L 14-K-J
A=Dog's Right arm
B=Dog's Left arm
C=Dog's Left leg
F=Sternal lead
D, E=Rt. Chest leads-(4th Interspace)
G, H=Left Chest leads
I=Rt. Bronchus lead
J=Esophagus lead
K=Lft. Bronchus lead

EXPERIMENT III - DIAGRAM I.

Experiment III (Fig. 3, A. B. C. Diagram I). *Complete insulation of the lungs without changing intrathoracic relationships or altering intrathoracic pressure.*

A. Three standard electrocardiograms were recorded. Successive control records were made by leading off from thorax, lungs and esophagus* as indicated in Diagram I.

B. 20 cc. Mineral oil† were injected into the right pleural cavity and same 14 leads taken as in *A.*

C. 20 cc. Mineral Oil were injected into the left pleural cavity and same leads recorded.‡

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* Esophagus and intrabronchial electrodes consisted of long well insulated wires with a small hook at the contact point. They were placed *in situ* by means of a bronchoscope. Contact electrodes were of the same material for any given experiment.

† Squibb, Resistance of this oil, measured between plates 3 mm. apart, equivalent to at least 600,000 ohms per sq. cm. through one millimicron thickness.

‡ At autopsy, on examining the tissues with hand lens, no break could be found in oil film surrounding visceral and parietal pleura.

In none of these curves is there any change in amplitude or contour. Thus, the lungs do not appreciably transmit the current to the surface of the body and must receive their potential through their pedicles.

Experiment IV (Fig. 4). *The pedicles of the lung as transmitting media of current from the heart.*

A dog was anesthetized. Right arm electrode placed in the middle bronchus of the left lung, the left arm electrode being placed in the left leg. Under positive pressure, the left chest was incised at the level of the fourth interspace, pulmonic veins, left pulmonic artery and a bronchial artery of the left bronchus were isolated and ligatures placed *in situ.* The pleural cavity was then bathed in oil and records taken after successively ligating and severing the individual vessels.

The changes noted in the various components of the electrocardiogram are definite. They can hardly be explained by increased pressure in the left ventricle.

Experiment V. Elimination of the possible factor of increase in ventricular pressure as a source of error.

Experiment IV was repeated, with the exception that two right arm electrodes were placed in the lower bronchus of the left lung (1 cm. apart) with the indifferent electrode on the left leg. The bronchial veins were isolated and ligatures placed *in situ.* The pulmonary artery was ligated distally and proximally and two electrocardiograms taken (Fig. 5, A-1 and B-1). The pulmonary veins were then tied and cut (Fig. 5, A-2 and B-2).

Results. The findings recorded in the first experiment are not difficult to understand. The various tissues excised are known to be excellent conductors. When the amputated part of the leg was allowed to remain on the operating table quite appreciably apart from the stump, but bathed in the same blood, the curves were not altered. *The extremities, therefore, do act as volume conductors, not only because of the relatively good conduction of each of the structures,* in contrast to the galvanometer circuit, but *also because of their remoteness from the heart.*

Approaching the problem by interfering with the several pathways in the vicinity of the heart over which the current might pass from the heart to the periphery, some noteworthy facts were disclosed. Almost insuperable difficulties were encountered in attempting to conserve the normal relationships in the chest and thus prevent a shift in axis of the heart or disturbance of lung contact. Experiment II, although carefully controlled by injecting air into the two chest cavities simultaneously, and by the use of the fluoroscope, is still subject to possible error. The chambers of the heart and the great vessels are not equally resistant and might react unequally to the same pressure. Then, too, one cannot be sure the heart has not rotated with removal of its support by the lungs.

To obviate this, Experiment III was performed which insulated the lungs without increasing intrathoracic pressure. Moreover, the leads were taken from the inner aspect of the lungs as well as the outer surface. The resultant records do not indicate decrease of amplitude or change in contour of the curves. Thus, the lung pedicles alone remain as selective paths for the current conduction, and in the last two experiments (IV and V) this fact is disclosed (Figs. 4 and 5). These electrocardiographic changes are definite and distinct. Could these changes be due to disturbances in arterial or ventricular pressure? As far back as 1876, Lichtheim[7] and somewhat later, Tigerstedt, demonstrated that three-fourths of the total number of branches of the pulmonary artery could be ligated, before arterial pressures were affected. Further, it has been shown that the lumen of the pulmonary artery could be compressed up to 60% of its capacity without affecting arterial pressure (Haggard and Walker[1]). On the other hand, Wiggers[7] observed changes in pressure within the right ventricle following the ligation of a single branch of the pulmonary artery.

In the last experiment (V) this possible factor is eliminated because that portion of the circulatory system is interrupted which could increase right intraventricular pressure. The deduction is, therefore, that *the electrocardiographic changes noted after ligation of various components of the lung pedicle represent interference with the passage of current through these tissues.* The pedicles offer paths of selection for the transmission of current from the heart to the lungs.

Conclusions. 1. Visual evidence is presented to confirm the accepted fact that the extremities act as volume conductors of the electrical potential generated in the heart.

2. The lungs transmit none of the differences in electrical potential registered in the electrocardiograms obtained by surface leads.

3. The lung pedicles act as the sole bridge for transmission of current to the lungs.

4. These pedicles offer selective pathways of conduction.

5. The recent controversies as to the advisability of using the apex of the heart or the fourth interspace just to the left of the sternum for the site of preference of the right arm electrode in Leads IV and V, seem to accept, *a priori*, the dictum that the chest is a volume conductor. We are convinced that the discrepancies seen in these controversies can be explained on the basis that the chest is not a volume conductor.

The authors are indebted for surgical assistance to Daniel Early, M.D., and J. J. Longacre, M.D., of the Department of Surgery, University of Cincinnati College of Medicine, and Cincinnati General Hospital.

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THE PROGNOSIS IN "POTENTIAL RHEUMATIC HEART DISEASE" AND "RHEUMATIC MITRAL INSUFFICIENCY."

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The prognosis of patients having an obvious diagnosis of rheumatic cardiac valvular deformity has been fairly well elucidated by many statistical studies. The prognosis, however, of young patients between the ages of 12 and 30 years, who have had rheumatic fever or chorea and present on physical examination either an entirely normal heart or at most an apical systolic murmur, has been far less thoroughly explored. The greatest diversity of views is found among the available statistical material in the literature as to the relative influence of chorea and of rheumatic fever in producing valvular lesions,[2] and few guides have been set up to indicate the probable future course of patients with slight rheumatic valvular damage.

These discrepancies in our knowledge have been in the main the result of two difficulties: the faulty memories of older patients with respect to their early rheumatic histories, and the difficulty of trying to follow closely a large group of essentially well people over a long period of years. However much the relative significance of a rheumatic history or of a systolic heart murmur may have been debated by clinicians in the past,[4] the large statistics of life insurance companies show that they have a definite influence on mortality rates.[1] It seemed worth while, therefore, to collect and analyze the records available in the cardiac clinic of this hospital as a contribution toward the evaluation of various factors operating in the production of chronic cardiac valvular disease.

Material. The present analysis consists of 225 cases with a history of rheumatic fever or chorea, but showing when first seen either nothing or at most a systolic murmur in the heart. Practically all patients were between 12 and 20 years when first seen (an average age of 13.8 years). With few exceptions the group consisted of patients who had had their rheumatic fever or chorea in a children's hospital, had been followed in a cardiac clinic there and then referred to our clinic upon reaching the age limit of 12 years, or who had been seen in this hospital with their first rheumatic infection and were subsequently followed in our clinic. Ten of the cases were referred to the clinic by school physicians because of the discovery of a heart murmur, but with no definite history of rheumatic fever or chorea and with the possibility of congenital heart disease being ruled out as far as possible. The onset of rheumatic infection was then assumed to coincide with the first discovery of the murmur.

The histories, therefore, are probably as reliable as is possible in such a series. All cases who had had severe cardiac damage with their earlier rheumatic infection were excluded. Patients with no clinical evidence of rheumatic activity were seen at intervals of 6 months to 1 year, and those suspected of activity, at shorter intervals. During flare-ups of rheumatic activity they were either placed in bed at home if the flare-up were mild, or in hospitals or convalescent homes for long periods if more severe. These patients then have had the best available supervisory care for the clinic class of rheumatic patients. The average length of time over which the 225 patients were seen in this clinic was 9.6 years (Table 1).

TABLE 1.—LENGTH OF TIME CASES WERE FOLLOWED.

Cases.	Time, years.	Average, years.
96 (41.8%)	1 to 4	2.7
91 (40.9%)	5 to 9	6.9
29 (13.2%)	10 to 14	11.6
5 (2.3%)	15 to 19	16.4
4 (1.8%)	20 to 23	22.0

For purposes of comparison, however, the patients were divided into groups expressing the years elapsed between each patient's first attack of rheumatic fever or chorea and his last visit to our clinic, which indicates the numer of years the rheumatic state may have existed in each patient, and it was upon this basis that the remaining analyses of this series were made (Table 2). The average time elapsed since the first attack of rheumatic fever or chorea for the whole group of 225 cases was 9.2 years. The sex distribution was 40% males, 60% females.

TABLE 2.—LENGTH OF TIME BETWEEN FIRST ATTACK AND LAST VISIT TO CLINIC.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.
No. of patients	32	95	72	20	6
Per cent of patients	14.2%	42.2%	32.0%	8.9%	2.7%
Average time elapsed	3.0 yrs.	7.0 yrs.	11.9 yrs.	16.5 yrs.	21.7 yrs.

Diagnostic Criteria. *Potential Rheumatic Heart Disease.* Patients with a history of rheumatic fever or chorea, but showing on examination either a normal heart or only a systolic murmur, if persistent, of not more than "Grade 1 intensity",[3] were regarded as having potential rheumatic heart disease.

Rheumatic Mitral Insufficiency. Patients with a history of rheumatic fever or chorea, and showing on physical examination a persistent apical systolic murmur of "Grade 2 intensity" or more were considered to have rheumatic mitral insufficiency. Those who showed at any time a systolic murmur which later disappeared were included under "potential rheumatic heart disease." Though our practice of grading the intensity of systolic murmurs has been in use only a few years, we have a fairly definite clinical impression that Grade 1 systolic murmurs frequently disappear later, and Grade

2 murmurs occasionally, but that Grade 3 murmurs are almost always persistent over many years.

Aortic Insufficiency. The prerequisite for this diagnosis was a persistent early diastolic bruit of any intensity at the base of the heart or along the left sternal border. In cases showing this diastolic murmur alone there is little doubt that it represented aortic insufficiency. In those also having mitral stenosis, the possibility of its being a "Graham Steele murmur" might be argued in some cases. Inasmuch as none of our cases were in failure such confusion can be disregarded.

Aortic Stenosis. This diagnosis was made in only one rheumatic patient who had an enlarged heart, aortic insufficiency and a loud, rough (Grade 4) systolic murmur and accompanying thrill in the second right intercostal space near the sternum.

Mitral Stenosis. The review of this series of cases emphasized the necessity of being conservative in making this diagnosis, a view which is to be elaborated in another paper by the authors. The diagnosis was made in cases with a regular heart rhythm on the basis of a rough mid to late diastolic or presystolic crescendo murmur ending in an accentuated first sound at the apex, or in cases with auricular fibrillation on the basis of a low pitched apical diastolic murmur of any duration. Cases with regular rhythm and low pitched apical diastolic murmurs shorter than the classical crescendo type and without marked accentuation of the first sound were labelled "question of mitral stenosis" unless the murmur had been present at least 4 years. A special effort was made to exclude the "normal third heart sound" from the latter category.

Tricuspid Insufficiency or Stenosis. No case suggesting tricuspid valve deformity was encountered in this series.

Only two members of the series are known to be dead, though many have been lost sight of for other causes. One case of mitral stenosis died suddenly in another hospital of acute pulmonary edema or pulmonary embolus. No autopsy was obtained. Another case of mitral stenosis and insufficiency and aortic insufficiency died in this hospital of subacute bacterial endocarditis. Postmortem examination confirmed the diagnosis.

Potential Rheumatic Heart Disease. This was the diagnosis made in 166 patients (73.8% of the series) on the basis of a normal heart when first admitted to the clinic or the subsequent disappearance of systolic murmurs originally present. In Table 3 these cases are compared according to the years elapsed since their first attack to ascertain the relative effect of single and repeated attacks of rheumatic fever or chorea in producing valvular deformity. Individual attacks of rheumatic fever and/or chorea within one year of each other are treated as a single attack.

It is evident that of 166 cases labelled "potential rheumatic heart disease," only 8 (4.8%) subsequently developed recognizable valve disease or a serious question of it. It is interesting that there seemed to be little difference in this respect between single and repeated attacks, the latter having only a slightly higher incidence of valve deformity. This would seem to indicate that following a single attack of rheumatic fever or chorea those patients who could be diagnosed "potential" had about a 96% chance of escaping valve disease, and if after 5 years following the attack nothing new developed, then there was practically 100% chance of their escaping serious cardiac damage. Following repeated attacks, the chances when the diagnosis was made were 94% if less than 10 years had elapsed since the first attack, and 100% after 10 years. It is difficult to escape the additional conclusion that these "potentials" formed a group whose hearts were relatively resistant to rheumatic infection.

TABLE 3.—POTENTIAL RHEUMATIC HEART DISEASE.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.	Totals.	
Cases remaining potential after a single attack	19	41	22	9	3	94	158
Cases remaining potential after repeated attacks	4	25	27	7	1	64	
Potentials after single attack who later showed permanent lesion*	2 ?2	..	..	..	..	4	8
Potentials after repeated attacks who later showed permanent lesion*	?1	3	..	..	..	4	

* Aortic insufficiency, mitral stenosis or questionable mitral stenosis (?2 = 2 questionable cases of mitral stenosis). The time interval shown is the time between the first attack and the appearance of the lesion.

Rheumatic Mitral Insufficiency. This group of 59 cases (26.2% of the series) presented on physical examination a persistent apical systolic murmur of sufficient intensity to warrant a diagnosis of mitral insufficiency. The effects of single and repeated attacks of rheumatic fever and chorea are compared for this group in Table 4.

TABLE 4.—RHEUMATIC MITRAL INSUFFICIENCY.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.	Totals.	
Persistent M.I.* alone following single attack	4	8	7	2	..	21	34
Persistent M.I.* alone following repeated attacks	1	8	4	..	..	13	
M.I. following single attack who later showed permanent lesion† . . .	3 ?1	?1	..	..	..	5	25
M.I. following repeated attacks who later showed permanent lesion† .	5 ?3	4 ?1	4 ..	2 ?1	.	20	

* Mitral insufficiency.

† Aortic insufficiency, mitral stenosis or ?mitral stenosis.

It is apparent that 34 (58%) of the cases of mitral insufficiency persisted virtually unchanged throughout the period of observation, while 25 (42%) subsequently developed serious valvular disease or a strong probability of it. Of the 26 cases showing mitral insufficiency following a single attack, 5 (19%) developed a serious lesion, all within 5 years after the infection. Of the 33 cases of mitral insufficiency with a history of repeated attacks, 20 (61%) later developed other definite or strongly probable valvular lesions, and the appearance of the lesions was fairly well scattered throughout the 20 years following the first attack. Therefore, patients showing mitral insufficiency following a single attack had an 81% chance of escaping further lesions under 5 years of observation, and 100% after 5 years. Similar patients with a history of repeated attacks, however, had only a 39% chance of escaping under 5 years after the first attack, with a progressively better prognosis the further removed from the initial attack during the next 20 years.

Relative Influence of Rheumatic Fever and Chorea. In an attempt to evaluate the relative effect of rheumatic fever and chorea in producing valvular damage, the cases in this series that developed unquestionable signs of mitral stenosis or aortic insufficiency or both were compared with the entire series, according to their histories (Table 5).

TABLE 5.—CASES DEVELOPING UNDOUBTED MITRAL STENOSIS OR AORTIC INSUFFICIENCY.

Following a single attack of rheumatic fever	3
Following a single attack of chorea	0
Following repeated attacks of rheumatic fever	9
Following repeated attacks of chorea	3
Following one or more attacks of both	9
No history of rheumatic fever or chorea	2

History.	Cases in entire series.	Cases developing M.S., A.I., or both.	%.
Chorea alone	44	3	6.8
Rheumatic fever alone	122	12	9.8
History of both	49	9	18.4
History of neither	10	2	20.0

The high percentage of valvular disease developing in the group with no history of rheumatic fever or chorea is obviously fallacious because these patients were all sent in to the clinic because of a definite suspicion of heart disease, whereas the remainder were followed simply because they had a history of chorea or rheumatic fever. It is then seen that the combination of chorea and rheumatic fever in the history was followed by much the highest percentage of valvular damage (18.4%), while that following rheumatic fever alone was not conspicuously higher than that following chorea alone (9.8 and 6.8%). It is interesting that in no instance did subsequent valvular damage follow a single attack of chorea. This might be construed as support for the contention[2] that chorea alone is incapable of producing rheumatic heart disease unless accompanied by rheumatic fever, even though the latter might be so mild as to be clinically unrecognizable. But the very much higher incidence of valve disease following a combination of rheumatic fever and chorea than from either alone (it is in fact about equal to the sum of the two diseases considered separately) might also support the view that there may be a "non-rheumatic chorea" indistinguishable clinically from the "rheumatic form." In this event, however, we believe that repeated chorea should probably always be regarded as of the "rheumatic form."

Relative Susceptibility of Valves in Relation to Sex. The well-known tendency of the mitral valve to be involved in females and the aortic valve in males was shown clearly in this series, though the total valvular involvement was about equal in the two sexes as shown in Table 6 (60% of the series were females).

TABLE 6.—VALVULAR INVOLVEMENT IN RELATION TO SEX.

	M.S.	A.I.	M.S. + A.I.	A.I. + A.S.	Total.
Males	3	5	2	0	10 (38.5%)
Females	9	3	3	1	16 (61.5%)

The theory has been advanced that the reason for the higher incidence of mitral stenosis in females may be that chorea is more likely to produce mitral stenosis than is rheumatic fever, and that chorea is more common in females. To investigate this possibility the cases of undoubted mitral stenosis, with or without aortic insufficiency, were analyzed according to history and sex and compared with a similar analysis of the entire series (Table 7).

TABLE 7.—COMPARISON OF MITRAL STENOSIS CASES WITH THE ENTIRE SERIES.

	Males.			Females.		
	Entire series.	M.S.	%.	Entire series.	M.S.	%.
Chorea alone	15	0	0.0	29	3	10.0
Rheumatic fever alone	57	3	5.3	65	3	3.1
History of both	15	1	6.7	34	5	14.7
History of neither	3	1	33.3	7	1	14.3

Again disregarding those cases with no history, it is seen that chorea or combinations of chorea with rheumatic fever were much more frequently followed by mitral stenosis in females than in males, while the incidence following rheumatic fever alone was somewhat greater in males than in females. This would seem to furnish some support to the above explanation of the more common occurrence of mitral stenosis in females.

There are some general practical inferences to be drawn from the above survey. One is led to the impression that the term "potential heart disease" is a valid term, for if after an attack of rheumatic fever or chorea there is no murmur or only a very faint systolic murmur (Grade 1), that patient stands an excellent chance of remaining well for many years. This is particularly true if the negative findings persist after 5 years. We have the distinct impression that some of these cases, however, even without any subsequent clinical recurrence of rheumatic fever, will develop mitral stenosis 10, 20 or 40 years later. This opinion is based on the experience of observing patients 50 or 60 years of age and older, who had their only rheumatic bout in childhood, first became aware of any heart trouble and showed signs of typical mitral stenosis at an advanced age.

Another point of interest is the subsequent course of those cases designated as having rheumatic mitral insufficiency on the basis of an apical systolic murmur of Grade 2 intensity or louder. We believe that although some will carry on indefinitely without any significant cardiac disability, some if not many will inevitably develop subacute bacterial endocarditis. These cases form a not insignificant group of patients who remain well for a great many years who may have been aware that they had a "harmless" murmur but who eventually pick up the fatal form of bacterial endocarditis. A few will slowly progress and develop mitral stenosis and others who only showed an apical systolic murmur may be found to have typical aortic stenosis many years later.

Summary and Conclusions. From an analysis of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years the following conclusions were drawn:

1. Of those cases diagnosed "potential rheumatic heart disease," 4.8% subsequently developed mitral stenosis, aortic insufficiency or both. With a history of only a single attack of rheumatic fever or chorea, these patients had a 96% chance of escaping valvular disease during 5 years after the attack, and 100% after 5 years. With a history of repeated attacks, the chances were 94% if less than 10 years had elapsed since the first attack and 100% after 10 years.
2. Of those cases diagnosed "mitral insufficiency," 58% persisted unchanged throughout the period of observation, while 42% subsequently developed mitral stenosis or aortic insufficiency. Those with a history of a single attack of rheumatic fever or chorea had an 81% chance of escaping further lesions before the lapse of 5 years, and 100% after 5 years. With a history of repeated attacks their chances were only 39% if less than 5 years had elapsed since the first attack, with a progressively more favorable prognosis as further years passed without the development of other lesions.
3. The occurrence of both rheumatic fever and chorea in the history was followed by a much higher incidence of valvular damage than following either disease alone, while that from rheumatic fever alone was about equal to that from repeated chorea alone. There were no instances of valvular disease following a single attack of chorea.
4. Some support was found for the theory that the greater tendency of chorea to produce mitral stenosis and the higher incidence of chorea in females is the explanation of the more frequent occurrence of mitral stenosis in females than in males.

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TRANSIENT NODAL RHYTHM FOLLOWING USE OF SULPHANILAMIDE.

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While it appears that sulphanilamide (para-aminobenzene-sulphonamide) has been established as a valuable therapeutic agent in combating infections due to hemolytic streptococci and some of the Gram-negative cocci, its ultimate range of use rests largely upon the severity and frequence of toxic effects. Among the ill-results caused by sulphanilamide have been reported: irritant effect on tissues of the urinary tract,[1] acidosis and depression of liver function (as determined by bromsulphalein),[7] neutropenia,[5] cyanosis, sulphemoglobinemia,[2] acute hemolytic anemia,[4] jaundice and urticaria,[6] and so on.

There have been no reports indicating a possibility of cardiac damage from sulphanilamide. In order that we may be able properly to select our patients to whom we plan to administer this drug, it is important that we record any adverse reactions. In addition to the aforementioned undesirable results, the writer presents a case which might establish the likelihood of cardiac damage resulting from the use of sulphanilamide.

Case Report. H. F., a physician, aged 27, had been suffering from an acute sore throat for 1 day. Throat culture revealed about 90% beta-hemolytic streptococci. Of his own accord, he took 80 grains of Prontylin (sulphanilamide) in 1 dose. Approximately 3 hours later he became nauseated, felt dizzy and had tinnitus aurium. He took 1½ grains of phenobarbital and went to bed. On the following morning, February 1, 1937, I was summoned to see him and he was complaining of pains in his knees and elbows, and in the small joints of his feet. There was no soreness of the throat.

The temperature was 98.6° F., pulse 80 and respiratory rate 20 per minute. The patient did not look ill. The general physical examination revealed very few abnormalities. The mucous membranes were of good color. There was no cyanosis or jaundice. The throat was slightly red, but did not appear acutely inflamed. Tonsils were absent. No enlargement of the cervical glands. The heart was normal in size. There was a soft systolic murmur heard over the entire precordium, but was loudest over the mitral area. The rhythm was regular. The lungs were clear to percussion and auscultation. The liver and spleen were not palpable. Weight, 160 pounds (72.7 kg.). No objective signs of joint disease.

The laboratory studies revealed the following: Throat culture: 90% beta-hemolytic streptococci. Blood: Red blood cells, 5,370,000; hemoglobin, 13.3 gm.; white blood cells, 9700. Neutrophils, 73%; lymphocytes, 22%; monocytes, 5%. Schilling count—stabs, 10; segmented, 63. Blood sedimentation (Cutler method) 15 mm. diagonal line.

Blood uric acid, 2.4 mg. per 100 cc. Urine: Specific gravity 1.007, faint trace of albumin, no sugar, acetone or diacetic acid, sediment normal.

He was placed on medical treatment administering large doses of salicylates for the joint pains. Felt quite comfortable, no sore throat, joint pains subsiding. On February 4, 1937, the patient became "cardiac conscious" and complained of irregularity in rhythm. Dr. E. H. Campbell was asked to do a complete otolaryngologic examination and he reported that the left maxillary sinus was slightly cloudy, the right one very cloudy, and the pharynx congested and showed evidence of excessive lymphoid tissue. The same day the temperature rose to 101°, pulse, 100, respirations 22.

Laboratory Studies: Blood: Red blood cells, 5,150,000; hemoglobin, 14 gm.; white blood cells, 14,400. Neutrophils, 66%; lymphocytes, 23%; monocytes, 11%. Schilling count—stabs, 12; segmented, 54. Sedimentation of red cells, 25 mm. Diagonal curve. Roentgen ray Studies: Heart normal size and contour. Lungs, negative; Teeth, upper right first molar showed evidence of some absorption of apices of roots.

The patient's general condition improved rapidly and he felt perfectly well, excepting that he was always conscious of some irregularity in cardiac rhythm. Discharged from the hospital February 10, 1937. Studies at the time of discharge: Temperature 98.2° F., pulse 70, respirations 18. Blood: Red blood cells, 5,300,000; hemoglobin, 13.8 gm.; white blood cells, 7600. Neutrophils, 67%; lymphocytes, 27%; monocytes, 4%; eosinophils, 1%; basophils, 1%. Schilling count—stabs, 9; segmented, 58. Sedimentation of red cells, 23 mm. Diagonal curve.

Patient went to Florida for 2 weeks' vacation and returned feeling well, but still complained of cardiac irregularity. Electrocardiographic tracings were done frequently and the findings were practically the same, in that there was a persistence of low voltage and nodal premature contractions.

No irregularity in rhythm was noted after April 20, 1937. The last tracing was taken on June 8, 1937, and is hereby presented to show return of normal rhythm, but evidence of myocardial degeneration persists.

During follow-up studies the blood pressure fluctuated from 130/80 to 160/90. Urine concentration studies (No. 1) 1.020, (No. 2) 1.019, (No. 3) 1.022. Eyegrounds by Dr. E. B. Spaeth: "Light streak on arteries of right eye more pronounced than normal. Increased tortuosity of vessels of smaller dimensions."

Comment. In view of the evidence that the patient was suffering from an infection, one naturally would wonder if the myocardial changes were not secondary to the infection. However, since there were definite symptoms of toxicity or idiosyncrasy after the ingestion of the drug, and since the one single dose was larger than is customarily prescribed, one seems justified in emphasizing the possibility of cardiac damage from the use of sulphanilamide. Also previous sore throats prior to the advent of sulphanilamide failed to cause any cardiac irregularity.

It is granted that the evidence presented is insufficient to prove definitely that sulphanilamide is capable of producing cardiac arrhythmias or cardiac damage. On the other hand, Griffith[3] had 2 cases that developed arrhythmias while taking sulphanilamide, which disappeared when the drug was discontinued. When Ratcliffe* gave a closely allied drug—Setazine (para-benzylaminobenzenesulphonamide) to a flamingo (weight 7 kg.) at the Philadelphia Zoölogical Gardens for a streptococcic ulcer on the thigh (5, 10 and 15 grains over 3 days), he found marked myocardial degeneration which he regarded as the cause of death.

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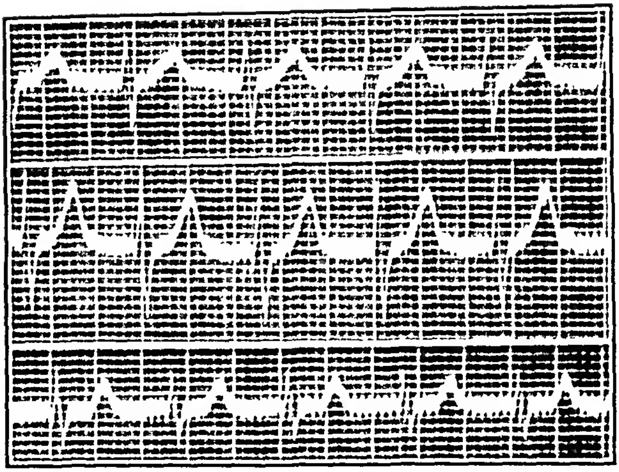

FIG. 1.—Tendency to right axis deviation, auriculo-ventricular nodal rhythm with the *P* waves coming after *QRS*, superimposed on *T*. Rate 118. (2/5/37).

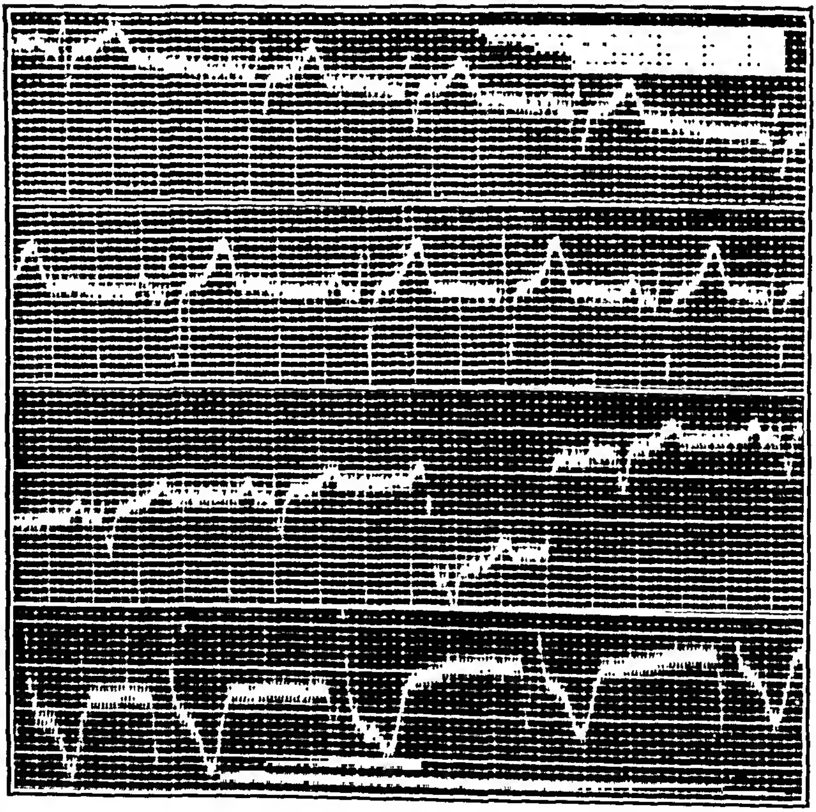

FIG. 2.—Note nodal premature contractions. (3/23/37).

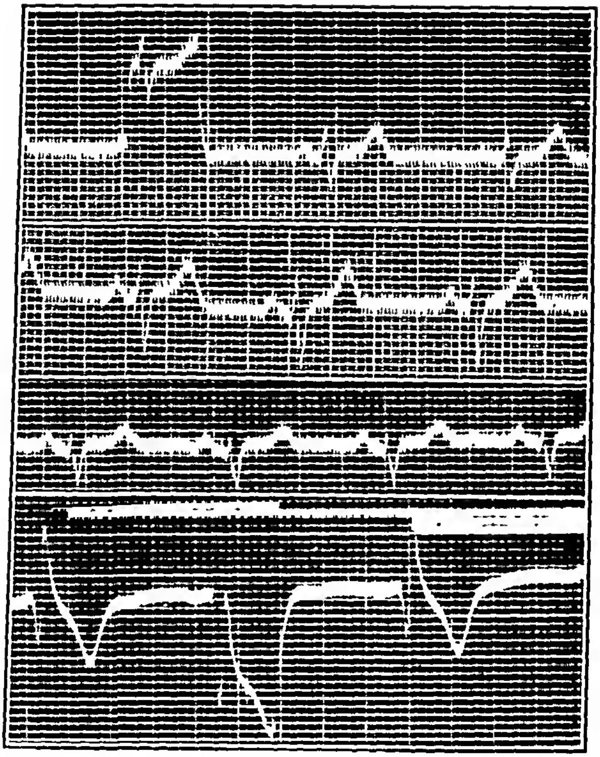

FIG. 3.—Note low voltage and normal rhythm. (6/8/37).

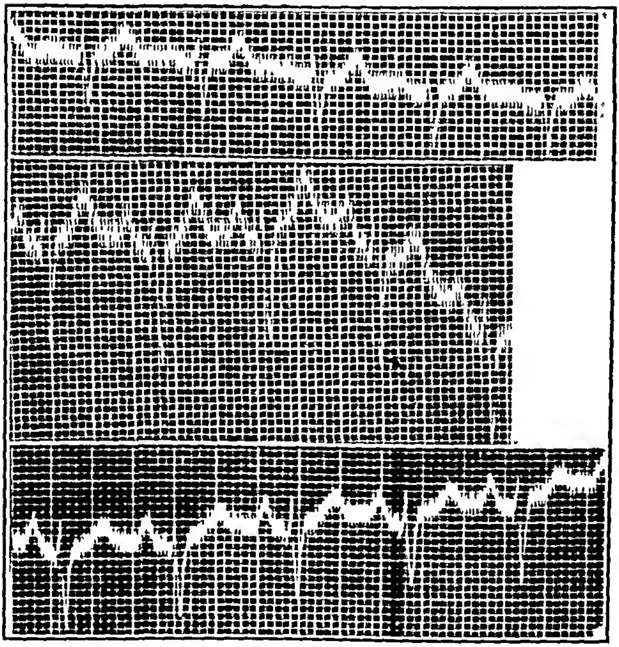

FIG. 4.—Note normal voltage. (1/23/34).

The patient here reported had, during his student days, occasionally developed attacks of paroxysmal tachycardia. An electrocardiogram taken at that time (January 23, 1934), is included for comparison with those taken after the ingestion of sulphanilamide.

The fact that the patient had manifested evidence of disturbance or irritability of the cardiac conductive system prior to having taken sulphanilamide, suggests that perhaps sulphanilamide is not apt to alter the rhythm unless there is some preëxisting irritability of the conductive system.

Summary. A case is presented of a physician who had taken 80 grains of Prontylin (para-aminobenzenesulphonamide) in 1 dose, which were followed by transient symptoms. Four days thereafter he developed arrhythmia and electrocardiograms revealed signs of myocardial degeneration and nodal rhythm.

Other evidence is cited to support the possibility that sulphanilamide is capable of producing myocardial damage.

While the evidence is insufficient to prove definitely that sulphanilamide was responsible for the cardiac disturbance in the patient herein reported, it indicates the need for caution in its administration to patients with cardiac disease, until further experiences are recorded.

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MANIPULATION OF GLUCOSE TOLERANCE BY DIET.

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The tolerance which an individual develops for glucose depends to a large degree upon the diet to which he has become accustomed. In the diabetic patient, the low tolerance for glucose may be increased by the use of a diet high in carbohydrate. In individuals with chronic hypoglycemia and increased glucose tolerance, there is a diminution in tolerance following restriction of intake of carbohydrate.

Hamman and Hirschmann[4] showed that in normal individuals "the ingestion of glucose in some way stimulates the mechanism of carbohydrate disposal so that the repeated ingestion of the same amount, causes a less marked hyperglycemia. The same stimulating effect is noted in diabetes; the second dose is followed by a less marked hyperglycemia and glycosuria. However, the difference between the effects of the two doses is less marked than in normals and varies in different stages of the disease."

It was demonstrated by Sweeney[7] and later by Himsworth[6] that in normal individuals the restriction of carbohydrate in the diet is followed by a loss of tolerance for glucose, whereas a diet high in carbohydrate results in an increase in tolerance.

Both Sweeney[7] and Greisheimer *et al.*[3] called attention to the fact that the glucose tolerance test is significantly affected by the character of food taken prior to the test.

The observations of Ellis[1] are very interesting in respect to the glucose tolerance in severe diabetes. In a small series of cases Ellis gave insulin at hourly intervals and glucose orally in amounts as high as 600 gm. per day. In all instances there was a striking reduction in the insulin requirement as compared to the doses necessary on a previously moderately restricted diet. There was a greater response in the younger, ill-adjusted patients than in the older and better adjusted ones. In this connection our own observations have shown repeatedly the necessity of lowering the insulin dosage in diabetic subjects receiving continuous intravenous glucose therapy.

Gibson[2] showed that diabetics who were controlled on a low carbohydrate maintenance diet had a remarkable improvement in tolerance, as indicated by a lessened requirement for insulin following 2 or 3 days of high sugar ingestion with increased insulin. Furthermore, he found that successive periods of high sugar diet at intervals of 4 or 5 days usually resulted in a progressive increase in tolerance, as judged by insulin requirements.

Weeks, Renner, Allen, and Wishart[8] placed 6 epileptic patients on very high fat, extremely low carbohydrate diets for 48 days. In every patient hyperglycemia gradually developed. The highest figure reached was 357 mg. per 100 cc.

Although the clinical implications are obvious both in respect to the dietary management of diabetes and of hypoglycemia, it is not the purpose of this paper to discuss in detail the practical application of these observations. We wish simply to show to what degree the glucose tolerance curve is altered as the result of diet in various conditions.

Two small groups of unselected cases are presented. Group 1 is comprised of 7 cases of chronic hypoglycemia. Glucose tolerance curves are employed to show that the use of low carbohydrate, high fat diets is followed by a decrease in tolerance and relief of symptoms. In such cases the tolerance tests show definite, and in some instances quite marked, elevation of blood sugar levels. In 2 subjects these rose to within diabetic range and were associated with glycosuria. In 1 of these patients whose intake of carbohydrate was subsequently raised, the sugar curve promptly fell again to within normal range.

Group 2 demonstrates marked improvement following the use of high carbohydrate diets in 5 cases of mild diabetes, as shown by glucose tolerance tests before and after treatment. In these cases all but 2 patients had not been controlled previously and this might have influenced the degree of change. One member of this group, after having been controlled on a high carbohydrate diet, was given a low carbohydrate, relatively high fat diet of equal caloric value and, after a month, a glucose tolerance test yielded distinctly higher blood sugar levels.

The dextrose tolerance test used in our cases is as follows: In the morning the fasting subject is given orally 100 gm. of glucose in 200 cc. of water and then only water is permitted until the completion of the test. Estimations of the blood sugar are made on the fasting blood and at intervals of ½, 1, 2, 3, and 4 hours after the ingestion of glucose, specimens of urine being obtained for estimation of sugar at the same intervals. At each of these times, an additional 300 cc. of water is given to insure the excretion of sufficient urine. Standard anticoagulants (calcium oxalate and sodium fluoride) are used and the blood sugar determinations are made on 1 cc. samples by a modified Myers-Bailey method.[6]

The cases studied are briefly summarized.

Case Abstracts. *Group 1.* CASE 1 (Fig. 1).—A man of 42 with a tentative diagnosis of hyperthyroidism had not improved following iodine therapy. This patient complained that nervousness, palpitation, tachycardia, dyspnea, and fatigue had been present for 1½ years. He had lost 20 pounds in weight over a period of 14 months. Examination revealed cool, moist, cyanotic hands and feet, tachycardia, and digital tremor. The basal metabolic rate was −8%.

He failed to improve on a schedule of rest, sedation, and high vitamin, high caloric diet. When he was seen again 6 weeks later, it was recognized that the symptoms usually occurred several hours after a meal. The glucose tolerance test showed evidence of increased tolerance, although 0.3 gm. of sugar was excreted between the first and second hour. His symptoms were reproduced by the injection of insulin.

A high fat, low carbohydrate diet (C. 85, P. 74, F. 180, Cal. 2256) was given and the tolerance test was repeated in 1 month, at which time he was clinically improved. This curve showed definite diminution in tolerance, but still a terminal hypoglycemia. Two months later he was symptom-free and "feeling better than for many years." The tolerance curve then was definitely of diabetic type, the 1-hour sugar level being 333 mg. per 100 cc. with no terminal hypoglycemia and a total glycosuria of 6.3 gm.

CASE 2 (Fig. 2).—In September, 1935, a woman of 41 presented herself, with severe headaches and attacks of upper abdominal pain. Weakness had been a prominent symptom recently and this was aggravated by short periods of perspiration, nervousness, and trembling. In June, 1935, a diet of C. 180, P. 56, and F. 75, Cal. 1619 had been prescribed elsewhere. A glucose tolerance test on July 14 showed a greatly increased tolerance for glucose. The glucose tolerance test repeated on September 6, 1935, gave

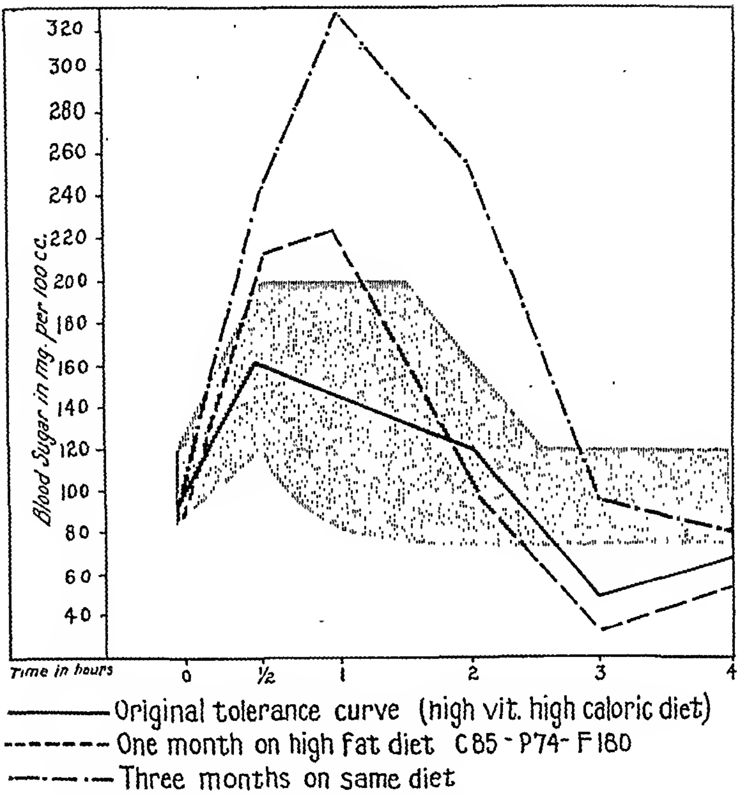

FIG. 1.—Decreasing glucose tolerance following low carbohydrate, high fat diet.

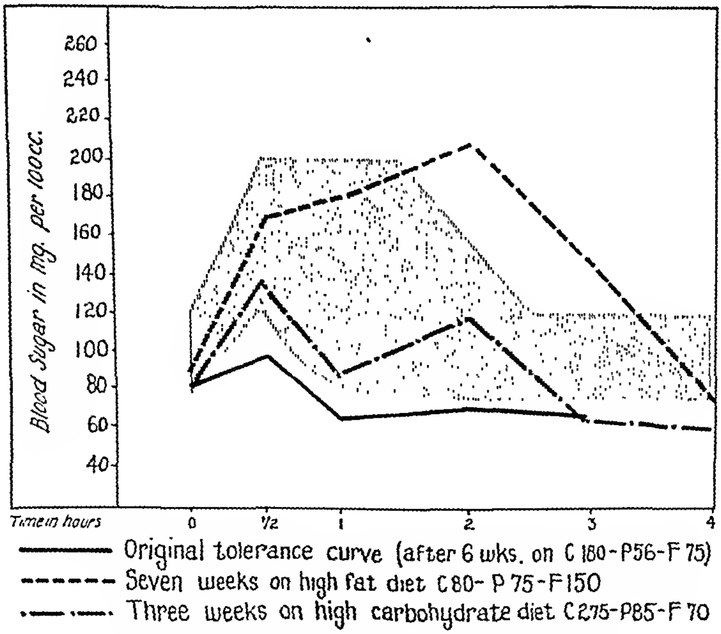

FIG. 2.—Tolerance decreased by low carbohydrate diet and increased by high carbohydrate diet.

the following levels in mg. per 100 cc.: 68, 140, 156, 141, 88, 45. A distinct hypoglycemic reaction occurred about the fourth hour.

On September 9, 1935, a cholecystectomy was done. The pathologic report showed chronic cholecystitis without stones. The clinical symptoms of weakness and perspiration persisted after operation and on September 21 she was given a weighed diet of C. 80, P. 75, F. 150, Cal. 1970. This was followed carefully while the patient was in the hospital and no more hypoglycemic reactions occurred. A glucose tolerance curve 7 weeks later showed a definite reduction in tolerance with a glycosuria of 0.63 gm. The fasting blood cholesterol level at this time was 272 mg. per 100 cc.

On January 4, 1936, a high carbohydrate diet (C. 275, P. 85, F. 70, Cal. 2070) was prescribed as a clinical test. At first the patient felt more energetic and had a better appetite. After 3 weeks a glucose tolerance curve showed a marked increase again in tolerance with no glycosuria. It is an interesting observation that the blood cholesterol level at this time had fallen to 208 mg. per 100 cc.

Case 3.—The patient, a girl of 14, had generalized convulsions. A glucose tolerance test showed the following levels in mg. per 100 cc.; 81, 107, 82, 75, 79, 65.

The patient was given a diet high in fat, relatively low in carbohydrate (C. 110, P. 75, F. 160, Cal. 2180). Six weeks later the tolerance curve was as follows: 85, 114, 171, 122, 107, and 107 mg. per 100 cc. of blood. Four months after beginning the diet she was still free from convulsive seizures and at this time her glucose tolerance curve showed some further decrease in tolerance. The levels were 88, 155, 161, 124, 115, 115 mg. per 100 cc.

Case 4.—A man of 47 complained of insomnia and periods of nervousness, associated with emotional instability, trembling, sweating, and groping for words. Two recent "faint" spells had been relieved by eating chocolate. He had lost approximately 35 pounds during the year. Physical examination failed to reveal any cause for his symptoms.

A glucose tolerance test showed increased tolerance with a hypoglycemic level at the third hour. It was as follows: 81, 113, 72, 85, 58, 73 mg. per 100 cc. of blood. He was given a diet of C. 110, P. 73, F. 117, Cal. 1785, which was increased 8 days later to C. 125, P. 88, F. 161, Cal. 2300. One month after the original glucose tolerance, a second test was as follows: 94, 154, 134, 103, 54, 72 mg. per 100 cc. It showed considerable reduction of tolerance; hypoglycemia, however, still persisted at the third hour. The patient was entirely relieved of his symptoms.

Case 5.—A woman of 25 had begun to have convulsive seizures of grand mal type at the age of 16. These had become increasingly more frequent. Physical examination revealed no cause.

On February 5, 1936, a glucose tolerance test showed the following levels in mg. per 100 cc. of blood: 68, 106, 102, 105, 74, 69. She was given a diet low in carbohydrate (C. 100, P. 65, F. 120, Cal. 1740) with frequent feedings. Two months later the fat content was raised to 153 gm. (Cal. 2040).

Three months on this regimen resulted in a reduced tolerance. The blood sugar levels were as follows: 87, 127, 161, 139, 80, 60 mg. per 100 cc. The urine contained a trace of sugar and acetone. Clinically, there had been no improvement, two additional attacks having occurred.

Case 6.—A woman of 20 complained chiefly of weakness, headaches, and dizziness. The symptoms were never related definitely to meals but could be relieved by a glass of sherry. She was short, slightly obese, the uterus was small, and pubic hair was scant.

The glucose tolerance was markedly increased with levels of 78, 98, 83, 61, 69, 48 mg. per 100 cc. of blood. She was given a diet of C. 72.5, P. 55, F. 122, Cal. 1608. Ten weeks later, considerable reduction of tolerance was noted except at the fourth hour which fell to the hypoglycemic level of 53 mg. and the patient experienced typical symptoms of hypoglycemia. The sugar levels were as follows: 93, 142, 116, 116, 109, 53 mg. per 100 cc. She had made definite clinical improvement.

Case 7.—A man of 29 had had attacks of weakness, nervousness, trembling, and at times hyperhydrosis for the preceding 9 years. He also suffered from insomnia, frequent headaches, and a constant tendency to stutter. Physical examination gave essentially negative findings. Five estimations of the basal metabolic rate over a 3½-year period gave normal findings.

A glucose tolerance test showed a markedly increased tolerance, the highest level being the fasting sugar. The values were 89, 88, 79, 54, 49, 70 mg. per 100 cc. of blood.

For 4 years he followed a low carbohydrate, high fat diet which was finally standardized to contain C. 100, P. 80, F. 200, Cal. 2520, taking 6 feedings per day. After 1 month and also 2½ months on this weighed diet, glucose tolerance tests were normal and exhibited considerable decrease in tolerance from the original curve. The levels after 2½ months on the above diet were 98, 169, 140, 69, 80, 88 mg. per 100 cc.

Three months later he was symptom-free but, for the purpose of investigation and with the patient's coöperation, his diet was radically changed to C. 275, P. 86, F. 95, Cal. 2300. Within 3 weeks the symptoms previously experienced were returning and 1 month after institution of this high carbohydrate diet, the tolerance test showed a definite increase in tolerance. The blood sugar levels were 117, 136, 82, 82, 70, 80 mg. per 100 cc. A high fat, lower carbohydrate diet was restored and soon he became free of symptoms once more. Symptoms may be reproduced at will by increasing the carbohydrate intake.

Group 2. Case 8.—A woman of 38 complained of a burning, constant pain, variable in intensity, over the precordial region of the 4th and 5th interspaces. This had been present for almost 3 years. She also complained of great nervousness and weakness. Her history suggested hysteria. Her mother died of diabetes at the age of 65.

Examination revealed slight thyroid enlargement and an area of tenderness over the left anterior chest wall corresponding to the site of the pain. She was believed to have intercostal neuralgia as well as diabetes mellitus.

The glucose tolerance test showed a mild diabetic type of curve with 1.5 gm.—total glycosuria. The levels were 82, 208, 256, 173, 141, 93 mg. per 100 cc. of blood. She was given a high carbohydrate, low fat diet, consisting of C. 250, P. 80, F. 60, Cal. 1860.

A glucose tolerance test made 10 days later showed a definite increase in tolerance although there was 2.58 gm. of glycosuria. The sugar levels were 94, 173, 191, 184, 120, 64 mg. per 100 cc. After the diet had been continued 2 months longer, the glucose tolerance test was normal and no glycosuria was present. The levels were 81, 110, 127, 94, 111, 68 mg. per 100 cc. She felt well at this time except for the chest pain.

Case 9.—A man of 59 had been found to have diabetes mellitus during a routine physical examination 3 years previously. Since then he had followed a modified low carbohydrate, high fat diet, approximating C. 120, P. 130, F. 120, Cal. 2080, and had been well controlled. Our glucose tolerance test indicated definite diabetes mellitus, with a glycosuria of 2.2 gm. The blood sugar levels were 120, 241, 297, 330, 214, 114 mg. per 100 cc.

He was in the hospital for 6 days for diabetic management. A diet of C. 190, P. 68, F. 100, Cal. 1932 was prescribed. No insulin was required, as diabetic control was complete.

The diet was gradually raised to C. 245, P. 93, F. 96, Cal. 2216 and the patient remained well controlled. This was repeated 20 months after the original tolerance test. He had followed the diet containing C. 245 for 12 months prior to this time. The test, though retaining a suggestion of lagging, was now normal, with levels of 102, 160, 160, 187, 96, 62 mg. per 100 cc. The urine showed a very faint trace of glucose but this was too small to estimate quantitatively.

Case 10.—A woman of 47 gave a history of chronic alcoholism of many years' duration. "All her life" she had suffered from "night-blindness." During the 18 months preceding admission she noticed increasing stiffness of the legs with uncertainty of gait. Her diet had been poor for 4 years and was entirely inadequate in meat and fruit. On examination, her skin was dry and rough. Her tongue was clean, red, and atrophic. Many crowned teeth were present. Hyperesthesia of the feet and legs and increased patellar reflexes were noted. The diagnoses were deficiency disease with peripheral neuritis, secondary to chronic alcoholism and diabetes mellitus.

She was given a high vitamin, high caloric diet with hydrochloric acid, brewer's yeast, haliver oil, and daily intramuscular injections of liver extract. During the next 2 weeks she ate poorly, due to poor appetite and because of the extraction of several teeth. Two weeks after admission a glucose tolerance test was made which showed a diabetic type curve with glycosuria of 0.3 gm. The levels were 110, 260, 288, 213, 160, 102 mg. per 100 cc. of blood. Three weeks after admission a weighed diet of C. 175, P. 65, F. 80, Cal. 1680 was prescribed and altered during the next 3 days to C. 205, P. 71, F. 80, Cal. 1824. After 2 weeks on this diet the tolerance test was entirely normal except for a faint trace of glycosuria. The sugar levels fasting and at 1, 2 and 3 hours were 83, 187, 133, 104, mg. per 100 cc.

In this case, several factors are present which modify the diagnosis of diabetes. In the first place she had existed on a very inadequate, almost starvation, diet prior to the time she entered the hospital, which was 2 weeks before the first glucose test. There were also distinct signs of deficiency disease and dental infection. Starvation diets, like diets low in carbohydrate and high in fat, cause a definite decrease in sugar tolerance.[7]

Case 11.—A man of 48 complained of drowsiness, fatigue, coldness, poor memory, dry skin, somnolence, and gradual weight gain of about 80 pounds during the past 20 years. He stated that his appetite was large. Examination showed only moderate obesity and the skin signs suggestive of hypothyroidism.

Urinalysis showed 3+ sugar. A glucose tolerance test was done which revealed a mild diabetic curve and glycosuria of 2.9 gm. The levels were 82, 192, 222, 226, 140, 75 mg. per 100 cc. of blood.

A diet of C. 205, P. 71, F. 80, Cal. 1824 was prescribed and ½ gr. of desiccated thyroid daily. After 7 weeks on this regimen, the glucose tolerance test was normal, he had lost 20 pounds in weight, and the symptoms were greatly diminished. The blood sugar levels were 94, 171, 170, 105, 84, 73 mg. per 100 cc.

Case 12 (Fig. 3).—A man of 50 was admitted for orthopedic care. Mild diabetes had been recognized 3 years before and he had limited the starch and sugar in his diet. Examination revealed that he was about 15 pounds overweight.

A glucose tolerance test showed a mild diabetic type of curve with a faint trace of glycosuria. He was given a diet low in fat and moderately high in carbohydrate which was gradually increased to C. 265, P. 83, F. 60, Cal. 1932. At first, glycosuria was noticed but this disappeared. After 1 month on this diet, a tolerance test showed definite increase in tolerance and was normal except for slight elevation at the third hour and a trace of glycosuria, insufficient for quantitative estimation.

The diet was then changed to one high in fat, low in carbohydrate, but of the same caloric value, consisting of C. 85, P. 70, F. 145, Cal. 1925.

After a month on this regimen the glucose tolerance test revealed a definite loss in tolerance at all periods up to the third hour.

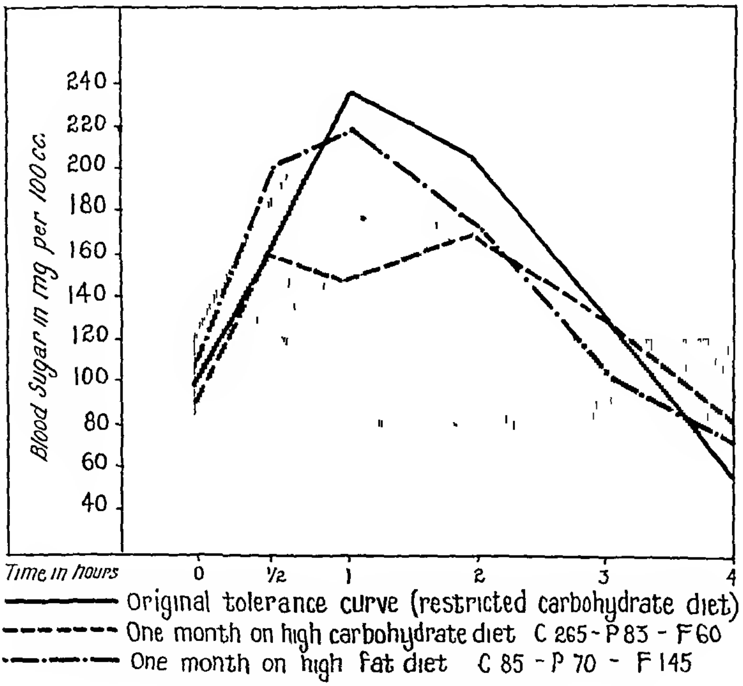

FIG 3 —Decreased tolerance on low carbohydrate diet and increased on high carbohydrate intake in a diabetic.

Summary. The glucose tolerance test has been used to demonstrate the change in tolerance which occurs following the use of various diets.

Two groups of cases are presented: One, a group of 7 individuals with chronic hypoglycemia; and the other, a group of 5 patients classed as mild diabetes mellitus.

In the cases of chronic hypoglycemia, there was a consistent decrease in tolerance following the use of low carbohydrate, high fat diets. Subsequently, in 2 of these cases increased tolerance followed the use of high carbohydrate, low fat diets.

In the cases of mild diabetes mellitus the tests showed an increased tolerance following the use of high carbohydrate, low fat diets. In 2 cases, the original diminished tolerance shown in our data followed the use of restricted carbohydrate intake for several years. In 1 of these the tolerance gained following the use of a high carbohydrate intake was largely lost 1 month after the institution of a low carbohydrate diet of equal caloric value.

Since tolerance of glucose is altered so definitely by various diets, a knowledge of dietary habits is necessary for proper clinical evaluation of the glucose tolerance test.

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DIETARY VERSUS INSULIN TREATMENT OF THE OBESE DIABETIC PATIENT.[*]

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The principle of undernutrition in the treatment of diabetes, announced by Allen in 1914, was regarded as so important before the discovery of insulin that the years 1914–1921 are referred to as the Allen era. However, since the introduction of insulin in 1921, the undernutrition principle has not received the attention that it deserves, especially as applied to the treatment of obese diabetic patients. The importance of this neglect may be realized when it is known that the majority of diabetic patients are overweight. In most of the clinics for the treatment of diabetes that we have observed, overweight diabetic patients with high blood sugar levels are usually *not* reduced, but are placed on diets that maintain their weights. Insulin must then of necessity be given, and, with the patient's weight kept at a high level, large doses are necessary.

Text-books do not bring out the fact that reduction in weight of obese diabetics will, in a large majority of cases, improve the tolerance for carbohydrate and total calories and reduce the level of the blood sugar to normal without insulin therapy. For example, Joslin appears to regard the amount of glycosuria as the criterion for giving insulin, regardless of the patient's weight. In the last edition of his book, this author[3a] says that he would give protamine insulin, 10 units before breakfast, to a previously untreated diabetic whose urine shows a red or yellow reduction with Benedict's reagent. Grafe apparently believes that the height of the blood sugar alone indicates the need for insulin in an uncomplicated diabetic, again regardless of the patient's weight. In his book on metabolic diseases, Grafe[2] states that: "If a (blood sugar) value of 0.3% or more is found, we may be sure that dietary restrictions alone will not suffice. The same is true if in spite of treatment a second analysis reveals a figure of about 0.2% without simultaneous renal or vascular disease. In such cases we are also dealing with the severe form of the disease which requires insulin."

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[*] Read at the Section on General Medicine of the College of Physicians of Philadelphia, October 25, 1937.

As has been pointed out by Duncan[1] diabetes is mild in any patient if that patient has never taken insulin and is considerably overweight, regardless of the initial blood sugar level. Guided by this principle, we have customarily given a low-caloric diet to uncomplicated overweight diabetic patients, so as to reduce the weight gradually (not more than 2 pounds a week), to somewhere near the calculated ideal weight for the patient's age, sex and height. With the weight reduction and simultaneous reduction of the total metabolism, the apparent need for insulin disappears. *These statements must not be taken to mean that we do not give insulin when it is needed.* All of our more severe diabetic patients (who are usually underweight) and the mild diabetics when complications develop are, of course, given insulin. However, the percentage of our diabetic patients taking insulin is relatively low. Joslin[3b] has estimated that 60% of the diabetics in this country are now taking insulin. In the Diabetic Clinic "B" at Pennsylvania Hospital, of 112 patients now active in the clinic only 33% (a little more than half of Joslin's estimated figure) take insulin. Some of these are recovering from complications and will not be permanent "insulin patients." Recent figures show that only 25% require insulin treatment permanently.

It should be emphasized that the group of patients under discussion is a large one. The percentage of diabetic patients who are obese is astonishingly high. Joslin[3c] found that of 4596 diabetics over 20 years, 78.5% of the men and 83.8% of the women were overweight at their maximum weights, and the percentages overweight at the onset of the diabetes were almost as high. No less than 16.5% of the men and 25.8% of the women were 40% or more overweight at their maximum weights. These percentages are about what we have found in our clinic. It is with these very obese patients, 40% or more overweight, that we are particularly concerned in this discussion. The advantages of treating this large group of diabetic patients without insulin are obvious. Not the least of these is the financial saving to the patient, or to the hospital if it provides insulin when the patient cannot pay for it.

The cases to be reported were all treated in the out-patient department where we had to rely on the patients' coöperation in following the prescribed diets. It is worth noting here that it is particularly important to restrict the large calorie carrier, fat, as well as, or in place of, carbohydrate. In general, too little attention is paid to the advantages of this restriction and its effect in reducing the blood sugar level. When the patient coöperated in following his diet, we found that the blood sugar level fell with the weight. If the patient refused to follow a low-caloric diet and maintained his high weight level, the blood sugar stayed high. To some of these patients we gave insulin, and found often that large doses (50 to 100 units daily) were needed to bring the blood sugar down to a normal level.

Illustrative Cases. Examples of obese diabetic patients belonging to two different groups are herewith presented. These cases are typical of all of the patients in each group. To save space and avoid repetition, the data on only a few of the patients in each group are included.

Group I. *Obese diabetic patients who showed a fall of the blood sugar level to normal with weight reduction.*

CASE 1.—A. FE., FEMALE, WHITE, AGED 51, HEIGHT 61 INCHES, IDEAL WEIGHT 135 LBS., 39% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	Diet. C.	Diet. Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
July 7, 1933	188	70	80	1100	2.1%	250
July 21	184	70	80	1100	0	177
July 28	181½	70	80	1100	0	144
August 11	179	70	80	1100	0	122
October 20	170	70	95	1300	0	115
January 26, 1934	167¼	70	85	1200	0	110
August 24	153	70	95	1300	v. ft. trace	113
March 8, 1935	148	70	105	1400	0	113
July 12	147	70	115	1600	0	110
October 9, 1936	157½	70	115	1600	0	110
December 10	156	70	140	1600	0	120
June 25, 1937	165	75	160	1800	0	113
August 13	161	75	160	1800	0	109

Summary. With a loss of weight of 9 pounds, the blood sugar level fell from 0.250% to normal. Subsequently, the carbohydrate tolerance was much improved. Even with an increase in weight of 14 pounds from the lowest level, the blood sugar stayed normal.

CASE 2.—D. D'G., FEMALE, WHITE, AGED 46, HEIGHT 59¼ INCHES, IDEAL WEIGHT 126 LBS., 49% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	Diet. C.	Diet. Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
March 25, 1932	186	70	80	1100	1.3%	238
April 1	178½	70	80	1100	0	152
April 15	174	70	80	1100	0	130
April 29	173½	70	80	1100	v. ft. trace	99
May 13	167	70	80	1300	0	88
July 8	155¼	70	80	1300	0	93
December 16	153½	70	120	1700	0	77
April 7, 1933	151	70	150	1700	0	76

Subsequently the carbohydrate in the patient's diet was increased to 250 gm. daily, the calories being kept at 1700. There was a gradual gain of weight to 174 pounds on August 13, 1937 (evidently the patient was exceeding her caloric allowance). The glucose tolerance test on January 27, 1936 showed a mildly diabetic curve, the highest blood sugar being 0.199% 1 hour after the administration of 100 gm. of glucose.

Summary. With a loss of weight of 9 pounds the blood sugar level fell from 0.238% to normal. Subsequently, even with an increase in weight of 21 pounds from the lowest level, the blood sugar stayed normal, showing a marked increase in the carbohydrate tolerance.

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* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 3.—F. H., FEMALE, COLORED, AGED 35, HEIGHT 60½ INCHES, IDEAL WEIGHT 124 LBS., 27% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
May 8, 1936	157	70	90	1200	1.6%	258
May 15	155	70	90	1200	0	192
June 5	152½	70	90	1200	0	169
July 24	147	70	90	1200	0	141
September 4	145	70	90	1200	0	111
November 6	143	70	90	1200	0	130
March 5, 1937	135	70	125	1400	0	134
April 16	137	70	125	1400	0	143
July 9	138	70	125	1400	0	161
September 3	139	70	125	1400	0	119

Summary. With a loss of weight of 10 pounds, the blood sugar level fell from 0.258% to normal. Subsequently, with an increase in the caloric allowance the blood sugars were slightly higher, but usually near the normal level.

CASE 4.—L. G., FEMALE, WHITE, AGED 62, HEIGHT 61½ INCHES, IDEAL WEIGHT 140 LBS., 37% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
February 19, 1934	192½	70	80	1200	Not done	238
March 23	188½	70	80	1200	0	170
April 13	185	70	80	1200	0	178
May 25	178¼	70	80	1200	0	143
August 3	168	70	80	1200	0	156
November 9	169	70	80	1200	0	137
January 16, 1935	162½	70	100	1200	0	126
April 12	165	70	100	1200	0	114
September 13	171	70	100	1200	0	122
January 10, 1936	174	70	100	1200	0	125
May 1	173	70	100	1200	0	114
November 13	174	70	100	1200	0	126
January 15, 1937	177	70	100	1200	0	133
June 25	174	70	100	1200	0	137

Summary. With a loss of weight of 25 pounds, the blood sugar level fell from 0.238% to nearly normal. Subsequently, with a slight increase in weight (apparently the patient was exceeding her caloric allowance) the blood sugar did not exceed 0.137%.

CASE 5.—A. FR., FEMALE,, WHITE, AGED 48, HEIGHT 63 INCHES, IDEAL WEIGHT 140 LBS., 46% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
August 13, 1934	205	80	90	1400	0.8%	225
August 24	207	72	90	1200	Ft. positive	185
September 7	203	80	85	1200	0	166
September 19	198	80	85	1200	0	169
October 12	195½	80	85	1200	0	151
December 7	189	80	85	1200	0	145
March 1, 1935	186	80	85	1200	0	132
April 12	185	80	85	1200	0	119
July 19	182½	80	85	1200	0	123
October 18	182¼	80	85	1200	0	103
March 20, 1936	184½	80	100	1200	0	118
July 10	184	80	100	1200	0	121
January 15, 1937	182	80	100	1200	0	115
April 16	183	80	100	1200	0	111

Summary. With a loss of weight of 20 pounds, the blood sugar level fell from 0.225% to normal. With no further loss of weight, the blood sugar has remained normal.

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* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 6.—A. C., FEMALE, WHITE, AGED 59, HEIGHT 61 INCHES, IDEAL WEIGHT 133 LBS., 42% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.		
May 12, 1936	189½	65	100	1200	3 plus	220
May 23	188	65	100	1200	1 plus	140
June 6	186½	65	100	1200	0	147
June 20	181½	65	100	1200	0	97
August 1	173	65	100	1200	0	80
October 8	173	65	100	1200	0	115
February 4, 1937	171½	65	100	1200	0	100
April 1	176	65	100	1200	0	95
June 17	165¼	65	100	1200	0	95

Summary. With a loss of weight of 7 pounds, the blood sugar level fell from 0.220% to normal. With a continued gradual loss of weight, the blood sugar has remained normal.

Group II. *Obese diabetic patients who failed to follow a low-caloric diet, and therefore needed insulin.*

CASE 7.—M. M., FEMALE, WHITE, AGED 56, HEIGHT 63 INCHES, IDEAL WEIGHT 138 LBS., 46% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.			
April 18, 1936	201	60	120	1125	20—20—20	0	250
May 16	202½	60	120	1125	20—20—20	0	152
July 11	198½	60	120	1125	20—0—20	0	170
September 24	197½	60	120	1125	20—0—20	4 plus	300
November 5	197½	60	120	1125	(35)—0—(10)	4 plus	247
December 24	201	60	120	1125	(40)—0—(10)	4 plus	160
January 21, 1937	197½	60	120	1125	$\boxed{40}$ —0— $\boxed{10}$	Not done	250
April 1	198	60	120	1125	$\boxed{45}$ —0— $\boxed{18}$	4 plus	174
April 15	195	60	120	1125	$\boxed{50}$ —0— $\boxed{50}$	4 plus	305
May 20	197	60	120	1125	$\boxed{60}$ —0— $\boxed{50}$	4 plus	200
June 24	194	60	120	1125	$\boxed{60}$ —0— $\boxed{50}$	4 plus	400

Note: ( ) represents protamine zinc insulin; ☐ represents crystalline insulin.

Summary. With failure of the patient to follow a low-caloric diet, the diabetes remained uncontrolled even with 110 units of crystalline insulin daily.

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* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 8.—H. D., FEMALE, WHITE, AGED 43, HEIGHT 62 INCHES, IDEAL WEIGHT 133 LBS., 9% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.			
July 3, 1934	144½	70	80	1200	None	1.6%	209
September 14	141½	70	80	1200	8—0—0	v. ft. trace	171
November 12	142	70	80	1100	11—0—0	0	166
January 7, 1935	145	70	80	1100	15—0—8	0	191
June 7	146	70	80	1100	12—0—10	0	254
October 14	153½	70	80	1100	11—0—10	0	159
January 6, 1936	156	70	80	1100	11—0—10	0	124
December 11	158	70	80	1100	8—0—12	0	235
January 22, 1937	158	70	80	1100	15—0—6	0	202
March 5	158	70	125	1400	(26)—0—0	0	141
May 21	163	70	125	1400	(45)—0—0	0	207
July 16	166	70	125	1400	(48)—0—0	0	191

Summary. With a weight gain of 22 pounds because of failure to follow a low-caloric diet, the insulin requirement rose steadily. Even with 48 units of protamine zinc insulin daily, the diabetes was not well controlled.

CASE 9.—E. P., FEMALE, WHITE, AGED 61, HEIGHT 62 INCHES, IDEAL WEIGHT 138 LBS., 6% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.			
November 9, 1934	146	70	90	1400	None	1.3%	265
November 16	146	70	90	1200	None	1.2%	234
January 4, 1935	145	70	90	1200	None	0	209
April 5	147	70	90	1200	None	0	186
October 21	150½	70	90	1200	None	0	200
December 6	151	70	90	1200	None	0.4%	155
June 19, 1936	146½	70	90	1200	None	1 plus	267
July 10	144	70	100	1200	8—0—6	0	195
November 20	154	70	100	1200	9—0—7	0	165
April 16, 1937	155¼	70	100	1200	(12)—0—0	1.4%	212
June 18	155	70	100	1200	(12)—0—0	1 plus	227

Summary. With a weight gain of 10 pounds, because of failure to follow a low-caloric diet, the diabetes was uncontrolled with relatively small doses of protamine zinc insulin.

Summary and Conclusions. We have presented case histories of obese diabetic patients which illustrate the following facts:

The great majority of obese diabetic patients, particularly those 40% or more overweight, do not need insulin. When such a patient is put on a low-caloric diet and his weight reduced, the blood sugar falls to normal without insulin. If such a patient is put on a diet that maintains his weight, large doses of insulin are needed to control the diabetes. Obviously, if simple weight reduction can achieve the same results as large doses of insulin, it is the treatment of choice in obese diabetic patients, especially as the loss of weight is in itself a desirable end.

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* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

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THE EFFECT ON THE BLOOD CELLS OF THE FETAL RAT PRODUCED BY THE INHALATION OF CARBON TETRACHLORIDE BY THE MOTHER DURING GESTATION.*

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Studies on the blood of fetal mammals have shown that their total number of erythrocytes per cubic millimeter is very low and that the size and volume of the erythrocytes are much greater than corresponding values for the adult. During gestation the total number of cells per cubic centimeter gradually increases and the size and volume of the cells gradually decrease; but at birth these values are far from approaching the corresponding values for adult blood.[17,31]

Wintrobe and Shumacker[32] compared these changes during the development of fetal blood with changes which occur in the blood of patients with pernicious anemia who are receiving some potent stimulus to blood formation. They thought that there must be some hemopoietic principles or stimulus which likewise controls the maturation of the fetal blood cells. Nothing is known regarding the possible hemopoietic factors which may be elaborated by the fetus. Gastric motility and gastric secretion of the fetal stomach have been studied,[33] but whether these secretions contain either intrinsic or extrinsic factors for regulation of the blood remains unknown. Jones, Shipp and Gonder have said that, "perhaps the factor is absorbed from the mother or it may be elaborated by the fetus." Wintrobe and his associates suggested that if a substance similar to Castle's antianemic principle[28] does influence the blood of the fetus, it probably comes through the placenta from the maternal circulation.

There are some data[27b] which show that human gastric juice, or hog gastric juice obtained from a fundic pouch, when injected into pregnant rats, will accelerate the maturation of the fetal erythrocytes. This would seem to indicate that the antianemic principle found in gastric juice may pass through the placenta to the fetus. Wintrobe, Kinsey, Blout and Trager, on the other hand, failed to find any changes in the blood of fetal rabbits when they injected liver extract into the adult pregnant rabbit.

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* Work done under the direction of Dr. G. M. Higgins.

The occurrence of macrocytic anemia is evidence of the lack of adequate antianemic principle. If this principle be supplied, as in the administration of liver, then the macrocytosis disappears. If the fetus depends for its antianemic factor upon the mother, then a reduction in the maternal stores might manifest itself in changes in the fetal blood.

The inhalation of carbon tetrachloride by white rats will produce marked hepatic cirrhosis accompanied by a macrocytic anemia.[16,27a] After 3 weeks of inhaling the drug for brief periods daily the number of erythrocytes per c.mm. drops from an average of 9.18 millions to 7.52 millions, and the size of the erythrocytes increases from a normal of 6.09 microns to 7.16 microns. Although there are no direct data to support the conclusions, the macrocytosis in these rats which have inhaled carbon tetrachloride may be due to a reduction in the available antianemic principle supplied by the stomach.

This present report covers the results of a study made on the blood of new-born rats that were born of adults which had been forced to breathe the fumes of carbon tetrachloride for brief periods each day during the period of gestation.

Methods. Female rats of the Wistar strain were mated. Insemination was established microscopically by the presence of spermatozoa in the vaginal smears. A total of 60 inseminated rats then breathed the fumes of carbon tetrachloride for periods of from 30 to 60 minutes daily from the second day following insemination to parturition.

Of these 60 rats, 12 lived to term and bore 86 offspring, the blood of which was studied as soon after birth as possible. The data assembled from studies of the blood of these new-born rats included determinations of the total number of erythrocytes and leukocytes per c.mm. of blood; differential leukocyte counts, including the percentage of myelocytes, metamyelocytes and granulocytes; the volume of packed erythrocytes; determinations of hemoglobin; the number of normoblasts, reticulocytes and thrombocytes, and the diameters of the erythrocytes.

Samples of blood were taken from the new-born rats by cardiac puncture, standard pipets being used. Hayem's solution was used as a diluent for the erythrocytes, and a 3% solution of glacial acetic acid with the addition of cresylecht violet (1 to 10,000) after the method of Kindred and Corey,[19] was used as a diluent for the leukocytes.

Standard hematocrit tubes, with heparin as the anticoagulant, were used for hematocrit determinations. Hemoglobin was measured in grams per 100 cc. of blood by means of the photoelectric method. The differential leukocyte, normoblast and reticulocyte counts were made from dry smears stained by the May-Grünwald-Giesma technique. The blood for the reticulocyte counts was mixed with cresyl blue, smears prepared and stained. For both the normoblast and reticulocyte counts the percentage of cells per 1000 erythrocytes was determined. Thrombocytes were counted by means of a micromethod in which the dilution of 0.1 cc. of blood was made in 1.9 cc. of a solution of sodium oxalate. Small vials were used as sedimentation tubes. The diameter of 100 erythrocytes for each of 15 animals was measured by projecting the cells of a dried smear with a camera lucida on to a micron scale at a magnification of 3000 diameters. The mean corpuscular volume, mean corpuscular hemoglobin, and the mean corpuscular concentration of hemoglobin were computed by the method of Wintrobe.

The number of erythrocytes per cubic millimeter of blood of the mother of each litter at parturition was also determined. Blood of the adult was taken from the ear vein, standard pipets being used.

Results. During the 3 weeks these pregnant rats breathed the fumes of carbon tetrachloride a definite anemia developed. The average erythrocyte count for the 12 rats (7.84 ± 0.15 millions) was very close to the figure of Higgins and Stasney (7.52 ± 0.15)[16] after treating normal male rats for 3 weeks.

TABLE 1.—COMPARISON OF DATA ON THE BLOOD OF NORMAL NEW-BORN RATS AND THOSE BORN OF MOTHERS SUBJECTED TO THE FUMES OF TETRACHLORIDE.

Stage.		Hematocrit, vol. %.	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes.	Thrombocytes, thousands per c.mm.	Normoblasts, per 1000 erythrocytes.	Erythrocytes, millions per c.mm.	Leukocytes, thousands per c.mm.
Normal	Number of animals	15	15	15	15	15	15	15
	Mean	47.3 ±5.5	26.9 ±0.24	91.2 ±0.5	427.9 ±17.0	0.313 ±0.20	3.27 ±0.32	3.22 ±0.13
	Standard deviation	31.8	1.4	3.2	98.8	1.17	1.81	0.76
	Coefficient of variation, %	67.3	5.2	3.4	22.8	373.8	56.6	23.6
After subjection of mother to fumes of CCl_4	Number of animals	15	15	15	15	15	20	20
	Mean	38.8 ±4.69	28.9 ±1.5	97.5 +2.5	562.4 ±13.4	0.32 ±0.19	2.45 ±0.05	6.23 ±2.72
	Standard deviation	8.1	0.2	0.4	23.4	0.13	0.41	2.12
	Coefficient of variation, %	12.06	5.5	2.5	23.9	353.1	1.65	34.1

TABLE 2.—PERCENTAGE DISTRIBUTION OF CELLS IN THE BLOOD OF NORMAL NEW-BORN RATS AND THOSE BORN OF MOTHERS SUBJECTED TO THE FUMES OF CARBON TETRACHLORIDE.

Stage.		Myelocytes.	Metamyelocytes.	Granulocytes.	Lymphocytes.
Normal	Number of animals	25	25	25	25
	Mean	23.0 ± 1.3	47.7 ± 2.2	16.7 ± 1.4	13.8 ± 1.1
	Standard deviation	9.8	16.0	10.7	8.0
	Coefficient of variation	42.7	33.6	64.3	57.8
After subjection of mother to fumes of CCl_4	Number of animals	25	25	25	25
	Mean	34.3 ± 2.4	44.3 ± 1.0	11.3 ± 1.0	11.9 ± 1.1
	Standard deviation	17.6	7.13	7.2	8.2
	Coefficient of variation	51.2	16.1	64.1	68.5

TABLE 3.—COMPARISON OF SIZE OF ERYTHROCYTES.

Stage.	No of cells measured.	Greatest diameter.			Least diameter.			Average diameter.		
		Microns.		C.V. %.	Microns.		C.V. %.	Microns.		C.V. %.
		Mean.	S.D.		Mean.	S.D.		Mean.	S.D.	
Normal	2100	9 24 ±0 05	3.8	40.7	8 60	3 7	42.6	8 80	1 2	13 0
After subjection of mother to fumes of CCl_4	1500	9 60 ±0 03	1.6	17.0	8 85 ±0 02	1.2	14.0	9 01 ±0 06	3 3	36 9

S.D. = standard deviation. C.V. = coefficient of variation.

TABLE 4.—CHANGES IN THE DIAMETER, VOLUME AND HEMOGLOBIN CONTENT OF ERYTHROCYTES IN EXPERIMENTAL MACROCYTIC ANEMIA.

Stage.	Mean cell diameter, microns.	Mean corpuscular volume, cubic microns.*	Mean corpuscular hemoglobin, micro-micrograms.*	Mean corpuscular concentration of hemoglobin, % *
Normal	9 24 ± 0.05	145 5	8 2	5 7
Anemia	9 60 ± 0 03	158 3	11 8	71 0

* Computed by the method of Wintrobe (1932).

The data derived from the blood of rats born of these 12 mothers, together with the data[5] assembled from new-born rats of mothers not treated with carbon tetrachloride are condensed in the accompanying tables (Tables 1–4). Most significant, perhaps, was the decrease in the number of erythrocytes per c.mm. and the decrease in the hematocrit reading (Table 1) from the normal levels. Coupled with the decrease in the number of erythrocytes there was an increase in the diameters of the erythrocytes and in their volumes (Table 4). There was an increase in the hemoglobin content of the erythrocytes and in the number of reticulocytes, normoblasts, leukocytes and thrombocytes (Table 1). There was a shift to the left in the cells of the myeloid line, and an increase in the number of immature cells in the circulating blood (Table 2).

When the percentage frequencies of the erythrocyte diameters were plotted (Fig. 1), the curve depicting the distribution of erythrocytes in rats born of mothers treated with carbon tetrachloride indicated the extent of macrocytosis induced in the fetus.

Comment. The effect on the erythrocytes in the blood of the developing fetus produced by the inhalation of carbon tetrachloride by the mother are comparable to changes which occur in the maternal blood. Normal maturation of the fetal blood was inhibited or greatly retarded, so that rats were born with values for erythrocytes that were characteristic of a late-term fetus rather than of a newborn rat.

Two possible explanations of the results of this study, in which macrocytic anemia was induced in new-born rats, need to be considered: Is the fetal anemia the direct result of the action of the drug upon the fetus, or is it due to a reduction in the maternal stores of the antianemic principle, thereby restricting the amounts made available to the fetus? Placental transmission of the drug is of course a probability, numerous reports[8,12,20,21,25] of the transfer of various substances across the placental barrier having been made. Studies on the transfer of such gases as oxygen and carbon dioxide across the placenta have been reported, and disassociation curves have been established;[1,4,9,10,13,18,22,23] but I know of no data on such transfer of carbon tetrachloride. It seems likely, however, that this gas may likewise enter the fetal blood stream.

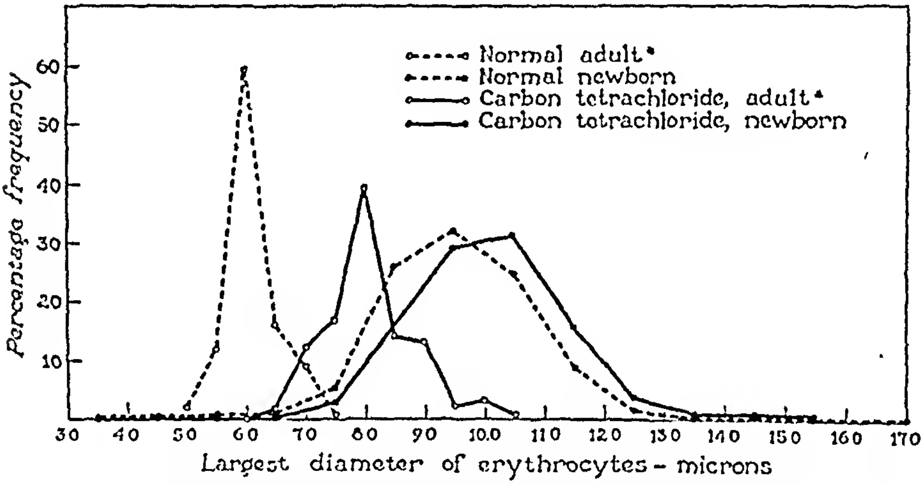

Fig. 1.—Curve of changes in percentage distribution of erythrocytes, according to size, in adult and new-born rats treated with CCl_4.

Since carbon tetrachloride is toxic and known to produce extensive changes in adult tissue other than hepatic cirrhosis and anemia, one should expect to find far-reaching changes in the tissues of the fetus if the drug had entered the fetal blood stream. Although unfortunately microscopic studies were not and cannot now be made, there was never any evidence of gross damage. The rats born of mothers which had received carbon tetrachloride were usually in good condition and there was no evidence of hepatic cirrhosis, hepatic damage being readily detectable even after very slight contact with carbon tetrachloride.

If the drug had caused the changes in the blood of the fetus, then one must postulate that the fetus elaborates the antianemic principle. No one thus far has shown that the fetus does elaborate its own antianemic principle. The extracts made of fetal livers, when injected, have not given consistent results. Goldhamer, Isaacs and Sturgis[11] reported a reticulocytosis of 17.6% when they gave human fetal liver, and Berglund reported a slight response to fetal calf livers. Wintrobe, however, could detect no response to fetal pig liver in patients who were suffering from pernicious anemia and who were in relapse. Nothing is known of the relation of the fetal stomach to hemopoiesis. It is not likely that the drug acted directly on the hemopoietic centers to destroy them. Higgins and Stasney observed a hyperplastic bone marrow, rather than an aplastic one, in animals receiving the drug daily.

It seems more probable that the effects induced in the fetus are the result of changes set up in the elaboration and storage of the antianemic factors in the mother. How carbon tetrachloride affects or reduces the principle in the adult rat is not clear, but it seems in some way associated with the degree of hepatic damage. The greater the hepatic damage the greater the degree of anemia. Sturgis,[29] in 1935, expressed the belief that the intrinsic factor normally produced by the stomach and stored in the liver was not available to the organism with a damaged liver because of its restricted storage capacity. These same conclusions were reached by Shumacker and Wintrobe.[26] Goldhamer, Isaacs and Sturgis[11] showed that extracts of a human cirrhotic liver elicited no reticulocyte response when given to a patient with pernicious anemia. Gastrectomy in the rat produced a hypochromic microcytic anemia[2] instead of a macrocytosis; but it may be that the intrinsic factor of Castle[28] is elaborated elsewhere in the intestines of rats as well as in the stomach. Carbon tetrachloride invariably upsets the gastro-intestinal tract of animals. Peristalsis is inhibited and food may remain in the stomach for days. It is possible that the drug restricts the elaboration of the intrinsic factor in the stomach, thus accounting for the macrocytosis which ensues. It is known, experimentally, that the factor present in human or hog gastric juice does pass the placental barrier and will affect the developing blood cells in the fetus.[2,27b] Thus there is reason to believe that, normally, this same transfer occurs and that the fetus depends for its hemopoietic stimulus upon the mother.

The high level of hemoglobin (Table 1) which was present in these rats may perhaps be accounted for by the hypothesis formulated by Whipple[30] and Heath[14] in their analysis of the hemoglobin content of the red corpuscle. They assumed that in pernicious (macrocytic) anemia, a deficiency in the stroma-building substance occurs, that all maturation is inhibited although hemoglobin formation takes place in a normal manner and, therefore, that the few cells which are being manufactured are saturated with hemoglobin and are in most cases enlarged in order to carry as much hemoglobin as possible.

The marked variation in the size of the erythrocytes (Fig. 1) agrees with the observation of Henry,[15] who also observed a difference in the size of the cells and the presence of a number of large ones, in his study of anemia in the new-born infant. The results of the present study (Fig. 1) showed the degree of macrocytosis and the range in diameters which have been produced in both the adult[16] and in the new-born rat following inhalation of the fumes of carbon tetrachloride.

The increase in the more immature cells noted in the differential leukocyte counts (Table 2) is similar to that observed by Klenerman,[21] who described a shift to the left (Arneth) in her study of the blood of infants. Brown, Morrison and Meyer[6] observed a leukocytosis, also with the shift to the left, in their studies of anemia in new-born infants.

Summary. Pregnant female white rats were rendered anemic by inhalation of the fumes of carbon tetrachloride. A cytologic study of the blood of the 86 rats born of these anemic mothers that had breathed carbon tetrachloride during gestation was then made and the results were compared with those of a study of the blood of 72 rats born of untreated mothers.

Macrocytic anemia developed in the fetus during intra-uterine development. This was evidenced particularly by a decrease in the number of erythrocytes per c.mm. of blood and by an increase in the diameters and mean corpuscular volumes of the erythrocytes. Other changes which have been observed include an increased hemoglobin content, reticulocytosis, thrombocytosis, leukocytosis, and a shift to the left (Arneth) in the differential leukocyte count.

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THE EFFECT OF IONTOPHORESIS WITH ACETYL-BETA-METHYLCHOLINE CHLORIDE ON THE RATE OF PERIPHERAL BLOOD FLOW.

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Although acetyl choline has long been known to be an extremely powerful vasodilator, its therapeutic usefulness for this purpose is limited by the dual nature ("nicotinic," "muscarinic") of its actions, by its great instability, and by the variety of other effects produced by it in addition to the desired vasodilation. Acetyl-β-methylcholine ("Mecholyl") is free of the first of these limitations because it is devoid of nicotinic actions, and less subject to the second because it is more stable than acetyl choline. It is, however, just as objectionable as acetyl choline from the standpoint of undesired effects (salivation, sweating, increased peristalsis, bronchial constriction, etc.) when the drug is absorbed into the circulation, and its therapeutic value as a vasodilator in peripheral vascular disease is correspondingly compromised. Kovacs and Kovacs[6a,b,7a,b,8,13] and Rutenbeck[12] have demonstrated that choline derivatives can be driven through the skin by means of an electric current (iontophoresis) and have opened the way for local therapy by these compounds.

Acetyl-β-methylcholine chloride, hereinafter termed ABMC, has had the widest use in this connection. The results point to the value of ABMC iontophoresis in treating some peripheral arterial disorders and arthritides, long-standing varicose ulcers,[13] scleroderma,[2] and thrombophlebitis.[10] The implication is that the clinical improvement results from increased blood flow produced locally in the part of the body that is treated; but as far as we are aware no direct evidence has been adduced as to the extent of such increase or even as to its actual occurrence. J. Kovacs[6a] reported an increase of 4° to 10° F. in the temperature of the limb treated, but the conditions under which these measurements were made are not clearly stated. If they took place after removal of the treating electrode, the rise in temperature might have represented only the influence of removal of the cooling effect of the solution with which the electrode was saturated. Or, later rises in skin temperature might have represented the removal of the cooling effect of sweating caused by the drug. Cohn and Benson[1] used a technique which minimized evaporation and found an increase in skin temperature that did not exceed 1° C. Evidence that vasodilation occurs is found in increased oscillometric readings following ABMC iontophoresis, in erythema and in an increase in capillary flow at the site of application,[7b] but blood flow measurements and information in respect to a local *versus* a systemic increase in blood flow are lacking. One of the advantages of iontophoresis over other methods of administering ABMC is that by it one may elicit considerable local vasodilation where it is therapeutically needed without producing disadvantageous systemic actions, but the effect should involve the major part of the vascular bed of the treated part. On the other hand, if iontophoresis should merely produce slight but relatively prolonged systemic choline effect, no greater in the treated part than elsewhere, this method would have no advantage over other less cumbersome ones.

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The object of the present investigation was to determine, by direct measurement, the effect of ABMC iontophoresis on blood flow in the limbs of normal individuals. A few corresponding observations have also been made on patients with peripheral vascular disease. A number of experiments were also made on dogs, but the results of these differ in some respects from those obtained in man, and so will be mentioned only briefly.

Method. To estimate the volume of blood flowing through a limb in a human subject we measured plethysmographically the rate at which limb volume increased when venous outflow was momentarily obstructed. Two hand plethysmographs of similar design were used. They are modifications by Freeman[3] of the instrument described by Hewlett and Van Zwaluwenburg.[4] Since they are made of metal it was possible to utilize the entire plethysmograph as the positive electrode for iontophoresis and thus to measure blood flow before, during, and after the treatment without altering the conditions of the experiment in any way. Since the experience of others (confirmed in our experiments on dogs) shows that direct contact of a metal electrode with the skin during iontophoresis produces burns, we lined the plethysmographs with rubber sheeting, $\frac{1}{4}$ inch thick, provided with numerous $\frac{1}{4}$ inch holes, and the metal at the wrist end of the plethysmograph was replaced with bakelite. The procedures used to seal the plethysmograph and to obviate changes in temperature of the part were those described by Freeman.[3] The experiments were carried out in a room maintained at constant temperature by automatic control. Changes in limb volume were kymographically recorded by a Krogh spirometer. To occlude venous outflow a wrist cuff was inflated to a pressure just below the arterial diastolic level. Measurements were made at intervals of 5 to 10 minutes. The apparatus was calibrated by injecting known volumes of fluid into the plethysmograph, and the volume of the hand was estimated by displacement of water so as to permit us to report the figures for blood flow in terms of cc. per 100 cc. of hand per minute.

The source of current for iontophoresis consisted of a 45 volt "B" battery and was controlled by a 10,000 ohm variable resistance. A 60 milliampere fuse was kept in the circuit. When two plethysmographs were used simultaneously separate ammeters and resistance units were used in each circuit. Current was turned on at about 4 milliamperes and gradually increased or decreased at a rate consistent with the comfort of the subject. Currents of 20 to 35 milliamperes were used for periods of 35 to 90 minutes. The negative electrode consisted of a sheet of copper screening 10 by 14 inches covered with several layers of gauze and one of light canvas. It was moistened with saline and applied to the back of the thorax. The plethysmograph was filled with 0.2% ABMC for iontophoresis, with tap water for control observations. To minimize the possible danger of escape into the subject of the 110 volt current used to operate the heating unit and stirrer of the plethysmograph, the latter was grounded, but this could not be done when two plethysmographs were used simultaneously.

Experiments were conducted on normal subjects and on patients in the same manner except that in the case of some of the normal subjects two plethysmographs, one on each hand, were used. The subjects were lightly clothed, with clothing adjusted in accordance with their comfort. The room temperature was kept constant during an experiment by automatic control, and the temperature of the fluid in the plethysmograph was kept nearly constant by a heater and a cooling jacket. Plethysmographic readings were taken at 5 to 10-minute intervals. The rate of blood flow fell during the pre-experimental period because of rest and because the room was somewhat cooler than the outside air. Controls were run in three different ways: (1) Blood flow was measured in only one hand using current but no ABMC; (2) blood flow was measured in both hands, with the drug and current on one hand and no current and no drug on the other; (3) blood flow was measured in both hands, with the drug and current on one and current but no drug on the other. When current was run through both hands the amount of current through each was made the same, and is reported in Table 1 as the amount in either hand, not as the amount at the source for the two leads.

The data to be presented were obtained on 6 healthy young adults and 3 young male patients with thromboangiitis obliterans and definite occlusive disease of the arteries of the hand. These patients had more severe obliterative changes in the feet than in the hands, but in each case there were sufficient changes in the hand to produce cold, blue fingers, decreased oscillations at the wrist, and a delayed filling of the hand as determined by an Allen test. B. G. (Table 1) had a thrombosed radial artery, as shown by surgical exploration. J. S. and B. G. had been sympathectomized in other limbs than those subjected to iontophoresis and to measurement of rate of blood flow. When the experiments were done none of the patients had open lesions on the hands.

Results. Iontophoresis through a plethysmograph containing 0.2% ABMC invariably caused a very marked increase in blood-flow in the treated hand (Table 1). As a rule the effect began after the current had been on for less than 15 minutes, reached a maximum within about 30 minutes, remained at that point as long as the current continued to flow, and began to decline almost as soon as the iontophoresis ceased. The duration of the increased blood flow after the current was turned off varied considerably, but as a rule recovery was practically complete within an hour (Table 1).* The patients with diseased arteries responded in the same general way as the normal subjects although the increase in blood flow was somewhat less marked in the patients, as would be expected. Thus in the normal subjects the initial flows varied between 1 and 14 cc. (average 4 cc. per minute per 100 cc. of hand) and between 12 and 32 cc. at the height of the ABMC effect. In the patients with obliterative disease the initial flows varied between 1 and 14 cc., those at the height of the drug's effect between 12 and 24 cc. No increase in blood flow was ever observed in the untreated (control) hand. Current without the drug produced either a slight rise or no rise in blood flow through the control hand. The drug without current had no effect on blood flow. The results are shown in Table 1 and representative graphs in Figs. 1 and 2.

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* The shortest duration was 30 minutes, the longest more than 105 minutes.

TABLE 1.—BLOOD FLOW IN THE HUMAN HAND UNDER ABMC IONTOPHORESIS.

Subject.*	Date, 1937.	Temperature (° C.).		Current.		Blood flow in hand (cc./100 cc. hand/min.).				
		Room.	Plethys.	mA.	Duration, min.	Initial.	Highest.	Recovery.		
								½ hr.	1 hr.	1½ hrs.
Normal, treated:										
C. F.	7/6	26	30.0 ± 0.3	20	35	1–2	12	1		
H. M.	7/8	26	28.5 ± 1.5	35	66	1	30	3	2	
C. F.	7/14	24	27.9 ± 1.3	30	40	2–11	25	18	16	17
C. F.	7/21	23	27.2 ± 0.7	30	40	2–4	26	7	7	4
H. P.	7/27	29	29.8 ± 0.3	30	46	7–14	19	19		
C. F.	7/29	26	30.1 ± 0.8	20	90	4–9	29	12	9	5
E. M.	8/5	25	28.7 ± 0.7	24	56	1–4	17	4	5	3
R. E.	8/11	24	29.6 ± 1.0	20	85	2–9	32	9	9	9
M. N.	8/12	24	29.6 ± 1.1	20	66	2–4	22	4	2	
Normal control:										
C. F. (current, no ABMC)	7/1	22	27.8 ± 0.0	25	62	1	2			
C. F. (current, no ABMC)	7/6	22	30.0 ± 0.3	20	44	3	3			
C. F. (current, no ABMC)	7/2	22	29.5 ± 0.5	30	86	1–3	7			
C. F.† (no cur., no ABMC)	7/14	24	27.9 ± 1.3	..	..	2	6	6	7	
C. F.† (no cur., no ABMC)	7/21	23	27.2 ± 0.7	..	..	1	1	2	1	
C. F.† (cur., no ABMC)	7/29	26	30.1 ± 0.9	20	90	1–9	4	7	5	
R. E. (cur., no ABMC)	8/19	25	28.8 ± 0.3	20	64	4–18	21	3		
Patient:										
H. H. (T. A. O. hand)	7/30	26	29.4 ± 0.4	30	46	10–14	24	18	17	
J. S. (T. A. O. hand)	8/4	25	28.5 ± 0.5	22	50	1	13	2		
B. G. T. A. O. hand)	8/7	24	28.9 ± 0.7‡	24	72	1–2	12	1	2	3
Reflex heat: (no cur., no ABMC)										
E. M.	8/2	24	28.8 ± 0.3	..	..	2	30	8§		
R. E.	8/18	24	29.0 ± 0.7	..	..	3–11	24	6§		

* Young adults, male except for "E. M."
† Simultaneous ABMC iontophoresis to opposite hand.
‡ Temperature in plethysmograph raised to 33.5° 1 hour after iontophoresis: no rise in blood flow resulted.
§ Fifteen minutes after treatment.

No conspicuous signs of systemic effects were ever observed. In several instances there was a slight increase in intestinal peristalsis and in one there was a slight fall in systolic blood pressure, but these were exceptional. Pulse rate was not significantly affected. The treated hand sometimes showed slight reddening and occasionally there was sweating of this hand for 1 or 2 hours after the treatment; but usually the prolonged exposure to the fluid in the plethysmograph produced thickening, corrugation, and whitening of the skin and neither hyperemia nor sweating could be detected. There was, however, a pounding sensation in the hand at the height of the ABMC effect. This was synchronous with the pulse and the pulsations of the fluid in the plethysmograph were visibly increased at this time. No burns resulted. In one case there was mild tanning of the skin area exposed to iontophoresis and this lasted several days.

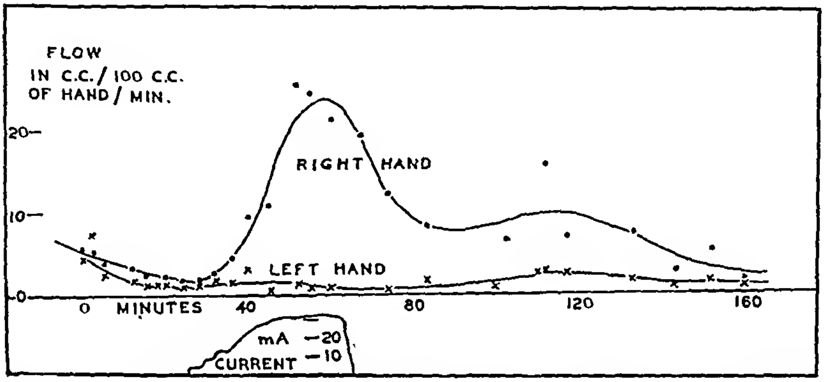

FIG. 1.—Representative blood flow in the hands of a normal subject. Right hand of C. F. (Table 1, 7/21/37) treated by ABMC iontophoresis, left not treated.

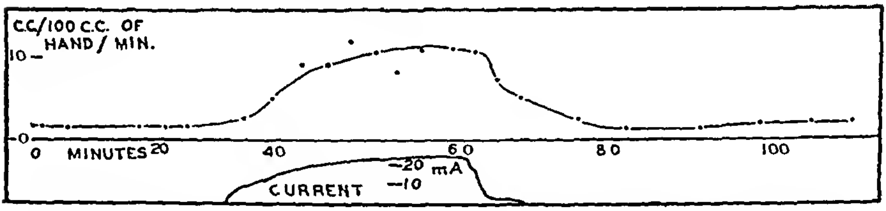

FIG. 2.—Representative curve of blood flow in the hand of a patient with obliterative disease of the arteries of this hand, hand (of B. G.) treated by ABMC iontophoresis.

These results fully confirm the belief that iontophoresis with ABMC produces marked dilation of the blood vessels in the treated part. The effect seems to be too great to be attributed to changes in the most superficial vessels alone and it is probably exerted upon deeper vessels as well. If the beneficial action depends entirely on an increased blood flow it occurs mainly in the part treated.

In 2 subjects ABMC iontophoresis was replaced by reflex vasodilatation in their hands produced by application of heat to the legs (Table 1, end). Blood flows of 30 cc. and 24 cc. per 100 cc. of hand per minute were obtained. On another day, ABMC iontophoresis produced blood flows of 17 and 32 cc. in these subjects. In 12 normal subjects Prinzmetal and Wilson[11] found that the average flow through the forearm was 3.6 cc. in response to heating the opposite arm in water at 45° C. They obtained in 17 normal subjects an average flow of 14.6 cc. during reactive hyperemia (temp. plethysmograph, 24° C.), 14.9 cc. when the arm was heated at 45° C., and 29.5 cc. during reactive hyperemia plus direct heat (temp. plethysmograph, 40° C.). The average flow in the hand in all our cases treated with ABMC iontophoresis was 23 cc. per 100 cc. per minute.

Studies in Dogs. Although the question of greatest interest was answered unequivocally by our studies in man, showing that blood flow is markedly increased in the treated part by ABMC iontophoresis with no, or with inconsiderable, systemic effects of the drug, a number of other questions of practical importance necessarily remained unanswered. Among these are the factors involved in the production of burns during iontophoresis, the part played by strength of current, strength of solution, and the size of the electrodes. In the hope of securing information on these and similar points, we carried out a series of 20 experiments on dogs anesthetized with chloralose and ether. Carotid blood pressure was recorded directly by means of a mercury manometer. ABMC iontophoresis was carried out on one leg.* Arterial blood pressure was reduced distinctly within several minutes when 0.2% ABMC and 6 or more mA of current was used, and other signs of the systemic effects of the drug (profuse salivation, increased peristalsis) soon became apparent. The fall in blood pressure did not depend upon the action of the anesthetic because it, as well as increased peristalsis, and increased salivation, occurred as promptly and as intensely in an unanesthetized dog.

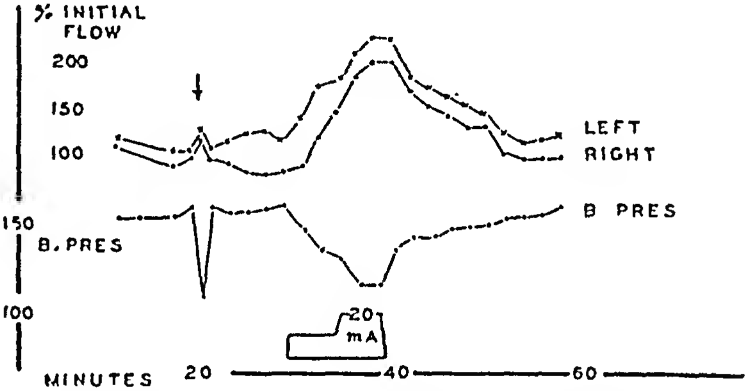

Fig. 3.—Dog 6, chloralose and ether anesthesia—blood flow in legs. ABMC electrode right leg, saline left. Same current through each leg (arrow indicates the time of injection of a minute dose of acetyl choline intravenously, with transient effect).

The observations on systemic effects on the whole confirm those obtained by Kotkis and Melchionna[5] on dogs and by Molitor[9] in rabbits, and yielded a certain amount of information which bears on the clinical use of ABMC iontophoresis. We found that the extent of the fall in blood pressure (and therefore the degree of effectiveness of the procedure) varied directly with the strength of the solution* (Fig. 4) and the amperage of the current (Fig. 5), and that the effect was due to the drug rather than to the passage of the current alone, since it was absent when saline was substituted for the drug. In addition, we found that varying the size of the positive electrode over a wide range did not affect the degree to which the blood pressure was reduced by given strengths of current and solution (Fig. 6). This, together with the fact that with smaller electrodes in man there was more local sweating and erythema than with larger ones, shows that a denser current (the same current through a smaller area) carries the same amount of ABMC into the body and increases the superficial local effect. Consequently, if one uses a very small electrode the amperage of the current must be reduced if a severe erythema or burn is to be avoided. On the other hand, if a very large electrode is used a current sufficient to produce the desired local effect might elicit severe general effects.

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* In the greater number of these dog experiments, blood flow through both femoral arteries (or veins) was measured by the thermo-electric method of Schmidt and Walker.[14] We found that under the conditions of the experiments ABMC iontophoresis produced systemic effects of the drug as promptly as it produced an increase in blood flow through the treated limb (Fig. 3). We were unable, by varying the strength of the drug, the amperage of the current, and the size and shape of the electrodes, even by using a metal-lined plethysmograph as the positive electrode, to produce in the dog the purely localized vasodilator effect that was so conspicuous in man.

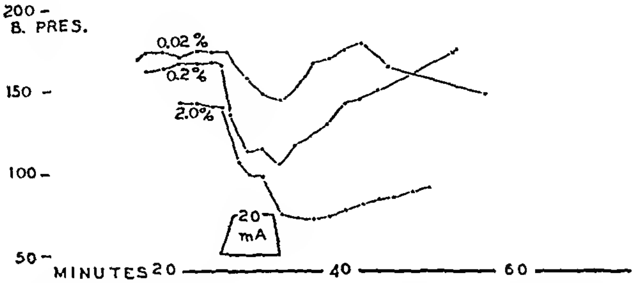

Fig. 4.—Dog 20, chloralose and ether anesthesia—effect on blood pressure of various concentrations of ABMC during iontophoresis. Curves show mean blood pressure.

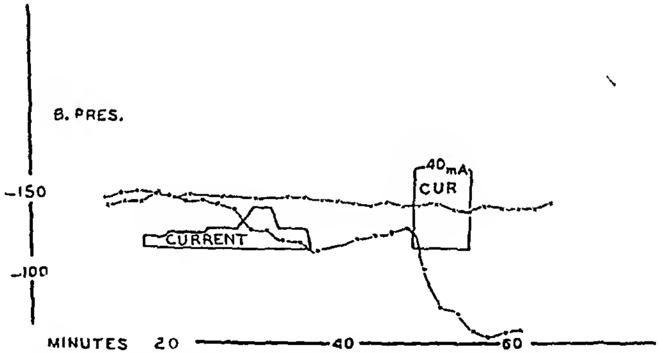

Fig. 5.—Dog 10, chloralose and ether anesthesia—effect on blood pressure of strength of current used during ABMC iontophoresis. Flat curve is control with no current. Curves show mean blood pressure. (Maximum current at left 20 mA, right 40 mA.

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* Kotkis and Melchionna found that a 0.5% solution of Mecholyl depressed the blood pressure to the same degree that a 0.012% solution did but was more effective than a 0.010% solution. Their results do not agree quantitatively with Molitor's or ours.

Studies on electrode burns in dogs bear out the conclusion that the local effect varies directly with the density of the current. With a current of 20 milliamperes when only the thin edge of a metal electrode was in direct contact with the skin, vesiculation occurred in 1 minute if it was the negative electrode, in 5 minutes if it was the positive. When the flat surface of the metal (8 sq. cm.) was used instead, the same current caused vesiculation in 4 minutes at the negative electrode, while no burn was produced in 20 minutes when the same electrode was positive. Evidently burns are more rapidly produced at the negative electrode than at the positive, and do not occur when the current is widely dispersed.*

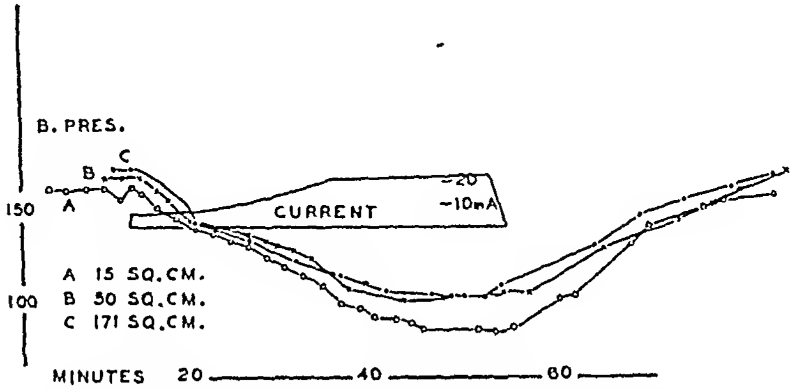

FIG. 6.—Dog 12, chloralose and ether anesthesia—effect on blood pressure of size of positive electrode during ABMC iontophoresis.

The simple rules learned to obviate burns are: 1, Do not use a small electrode unless the current is appropriately decreased; 2, never let metal touch skin; 3, do not regard the negative electrode as unimportant, but keep it as large as possible and be particularly careful to keep its metal from touching skin.

Summary. 1. Numerous measurements of blood flow in the hands before, during, and after acetyl-β-methylcholine chloride iontophoresis were made in human subjects. There was consistently a great increase in blood flow.

2. Blood flow in the affected hands of 3 patients with obliterative disease of the arteries was greatly increased by ABMC iontophoresis. There was some lasting effect in these patients as well as in normal subjects.

3. Systemic effects of the drug were rare. In the untreated hand there was no increase in blood flow. Current alone produced a slight increase in flow. ABMC without current did not alter blood flow.

4. In the two subjects studied, ABMC iontophoresis increased peripheral blood flow to about the same extent as did reflex vasodilatation. The effect by iontophoresis was more lasting. The therapeutic possibilities of reflex vasodilation have not been tested.

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* Dr. Hans Molitor tells us that he has seen much the same, and has seen burns produced when a cloth-covered electrode becomes dry in all but several small spots. Burns occurred at these spots.

5. In dogs systemic rather than local effects of the drug predominated. Whether this is a species difference, or is related to the difference in experimental conditions is not known. The systemic effect varies with the concentration of the drug and the strength of the current, but is independent of the size of the electrode within the range of sizes used. In anesthetized dogs there was usually a mild, generalized increase in peripheral blood flow during ABMC iontophoresis.

We wish to thank Prof. Carl F. Schmidt for helping us to assemble and use the thermostromuhrs, Dr. Norman E. Freeman for lending us his plethysmographs, and Merck & Co. for donating the drug (Mecholyl).

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CHANGES IN BLOOD LIPIDS DURING INSULIN TREATMENT OF SCHIZOPHRENIA.

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Sakel's insulin-hypoglycemia treatment of schizophrenia, which has been carried out on a number of patients in this hospital (Cameron and Hoskins[4]), afforded an opportunity to study the acute and chronic effects of large repeated doses of insulin on various physiologic variables in the human organism. This report deals with the variations of blood lipids during the course of the insulin treatment in 16 cases, 5 of whom showed a good remission during the treatment. The acute physiologic effects of insulin on the post-absorptive level of blood lipids were studied during the course of the hypoglycemic reaction. The chronic effects of repeated doses of insulin on blood lipids were studied at intervals of 2 weeks during the course of the treatment, and the variations occurring were correlated with the clinical status of the patient and with changes in body weight. If a good correlation between blood lipid levels and clinical status could be found, we might have a physiologic index of a patient's progress under various regimens of treatment.

Numerous attempts have been made to determine whether or not there is an abnormal lipid metabolism in schizophrenia. These attempts have consisted in the study of the absolute level of blood lipids in patients compared with that in normal controls, the comparison of early cases with long-standing cases, and the correlation of the changes in lipid level in patients with variations in their emotional content or clinical status. Stenberg,[22] from a study of previous literature, concluded that a difference in the blood lipid level of schizophrenic patients and normal controls had not been demonstrated. He criticized the previous work for the use of inadequate chemical and statistical methods and the small number of cases. Using Bang's methods, Stenberg compared the total cholesterol and total fatty acids in 62 female and 9 male patients, with 25 female and 9 male controls. He was not able to find a statistically significant difference between patients and normals, although the mean blood lipid levels were slightly higher in the patients. Brice,[2] using Bloor's methods, compared 62 schizophrenic patients with 25 normal controls. The mean values for total cholesterol and total fatty acids were slightly lower in the patients than in the normal, but the difference was not statistically significant; however, he claimed that his data presented evidence of a real depression of blood lipids. A report from this laboratory by Looney and Childs[12] indicated that schizophrenia might be characterized by a slight depression of the blood cholesterol. This conclusion was based on a study of 50 male patients and 26 normal controls, using the method of Myers and Wardell.[16] Further intensive studies have shown a seasonal variation of blood cholesterol in patients (Jellinck and Looney[9]). Unpublished data indicate that when this seasonal variation is taken into account by studying patients and normals in pairs, there is no significant difference in blood cholesterol between the two groups. Because of the great intraindividual variation of blood lipid from day-to day and the even greater interindividual variation in both patients and normal controls, only a very large difference would be statistically significant. An essential aspect of this investigation is the determination of the intraindividual changes of the blood lipids during the psychosis and after recovery.

That the duration of the illness and emotional factors may play a part in determining the absolute levels of blood lipids in schizophrenic patients has been indicated. Sharpe[20] thought that blood cholesterol was decreased about 25% below normal early in schizophrenia and then increased to 30% above normal in long-standing cases. Lipid phosphorus did not show any significant variation from the normal. In 24 cases of less than 1 year's duration, Stenberg[22] found that blood cholesterol and total fatty acids were higher than normal and these values returned to normal during remission. In 38 cases of long duration, the mean blood lipid levels did not differ from the normal. However, those patients with heightened emotions showed high blood lipids; those with dulled emotions showed low values; and those without emotional disturbances showed normal values. In contrast to this apparently direct relationship between the blood lipid levels and the emotional tone of the patients, Duncan[6] thought that there was an inverse relationship between emotional tone and blood cholesterol. High values were found in 47 of 76 patients who were in quiet or dull mental states, and low values were found in 38 patients who were in confused or excessive emotional states. During periods of excitement, lower cholesterol was found in 21 of 25 patients than during intervals of quiet or apathy. Brice,[2] corroborating Stenberg's work, found that the depression of the level of blood fats was most pronounced in the apathetic, stuporous types of cases. Emotionally excited cases had higher values. Looney and Childs[12] did not find any significant relation between blood cholesterol and the emotional status of the patients.

Experimental Methods. The technique of the insulin hypoglycemic treatment, following Sakel's method, has been described by Cameron and Hoskins.[4] The treatment consisted in giving 20 units of insulin subcutaneously to the fasting patient. In some cases this was given daily and in a few cases twice daily. The dosage was gradually increased until a hyperinsulin reaction was produced, and thereafter the dosage was dependent on the clinical progress of the patient. In the majority of cases the dosage was increased until coma was produced. The hypoglycemic reaction was terminated by the administration of sugar when the most desirable mental state of the patient was reached. The clinical progress of the patient was estimated from day to day by the psychiatrist. Each patient was observed over several hours each day, and, following the treatment, was interviewed. The patient's affective response, his capacity to mix with others, his work output, his interest in personal appearance, and his sex attitude were taken into account. The psychiatrist's observations were checked against the daily reports of the nurses and periodic reports of the Occupational Therapy department. The relatives were also interviewed and their statements considered in reaching a final judgment.

Blood lipids were studied before beginning treatment and at intervals of 2 weeks to 1 month during the course of the treatment. Blood samples were taken in the morning, in the postabsorptive state (14 hours after the last meal) before the insulin injections. Since the blood samples were taken at least 20 hours after the preceding insulin injection, the acute effects of the insulin hypoglycemic reaction on blood lipids should have subsided. To study the effects of the acute hypoglycemic reaction itself on blood lipids, a few blood samples were taken during the reaction, usually 2 to 3 hours after the insulin injection when the patient was in coma and the blood sugar at a low level. Phospholipid, total lipid, and total cholesterol were determined on whole blood by Bloor's method.[1a,b]

Results. In 14 of the 16 cases studied, a significant rise in the blood lipids occurred during the early weeks of treatment. The mean rise in these cases is shown in the accompanying chart. This initial rise is statistically significant for phospholipid, total lipid, and total cholesterol.* Of the 14 cases who showed an initial rise of blood lipids during the early weeks of treatment, 9 showed a return to the pre-medication levels as the treatment proceeded.

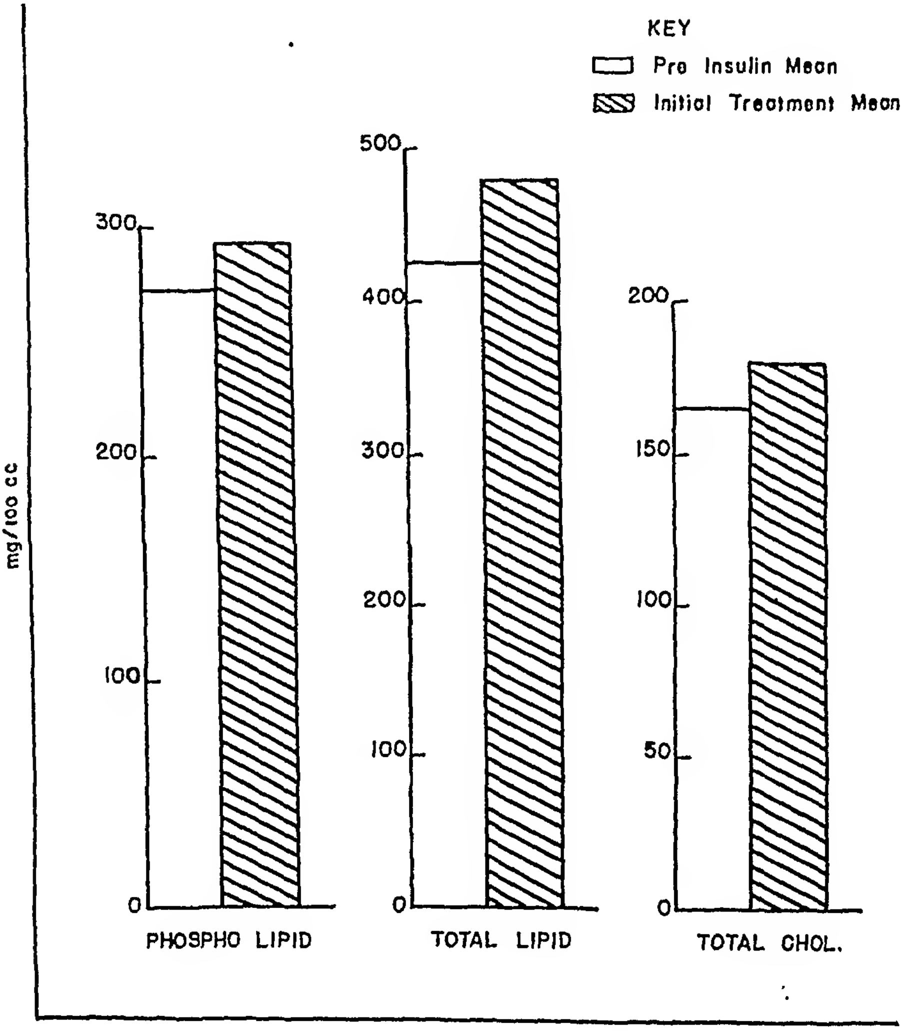

CHART 1.—Mean rise in blood lipids during initial insulin treatment.

Following the initial rise only random variations about the premedication level occurred. Minor variations in the clinical status of the patients were also noted, but no significant correlation between the clinical condition and the blood lipid variations could be recognized. Most of the cases also showed a considerable gain in weight during the treatment, but no significant correlation between weight changes and the blood lipid variations was apparent.

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* The significance was tested by means of Fisher's "t." The probabilities attaching to the "t's" show that such differences as observed here would occur by chance less than once in 100 trials.

Five of our cases showed a good remission during the treatment. These 5 cases all showed a significant rise in blood lipids over the pre-medication level. The accompanying table shows the means and ranges of phospholipid, total lipid, and total cholesterol in these cases during the initial state before recovery and during remission. The means were calculated from at least three determinations, at intervals of 2 weeks. The mean values for phospholipid, total lipid, and total cholesterol were significantly higher during remission than in the initial state.

TABLE 1.—MEANS AND RANGES OF BLOOD LIPIDS IN PATIENTS BEFORE AND AFTER REMISSION.

		Phospholipid, mg. per 100 cc.		Total lipid, mg. per 100 cc.		Total cholesterol, mg. per 100 cc.	
Patient.		Mean.	Range.	Mean.	Range.	Mean.	Range.
1.	Initial	256	250–260	384	380–405	147	138–155
	Remission	276	254–305	435	390–465	163	155–177
2.	Initial	225	220–230	375	365–380	142	140–144
	Remission	283	266–300	455	430–480	154	153–155
3.	Initial	277	260–285	405	380–420	166	160–168
	Remission	288	285–291	483	465–510	206	184–217
4.	Initial	281	270–290	505	490–520	180	175–185
	Remission	343	330–370	593	580–605	194	185–208
5.	Initial	287	270–302	433.	420–450	169	163–174
	Remission	316	300–332	543	475–605	200	180–230

The effect of insulin on the postabsorptive level of the blood lipids was determined 9 times on 5 patients. The blood lipids were studied before and 2 to 3 hours after an insulin injection. Only minor and random variations from the postabsorptive level were found during the course of the hypoglycemic reaction so that no data are presented. Reports of the effects of insulin on the postabsorptive level of blood lipids are variable. In normal men, Christomanos[5] found that blood fats fell slightly after insulin, but Bruger and Mosenthal[3] did not find any consistent effect of insulin on plasma cholesterol. Rony and Ching[18] and Miller[15] could not demonstrate any significant effect of insulin on blood lipids. However, a rise was reported by White[24] and a fall by Wertheimer,[23] Schmidt and Ssaatchian,[19] and Himwich and Spiers.[7] In rabbits, Page, Pasternak, and Burt[17] reported a fall in serum lipids after insulin. It is apparent that the effects of insulin on the postabsorptive level of blood lipids are not very marked or consistent, the contradictory results reported by various workers depending on the use of different and often an inadequate number of experimental subjects, various dosages, and various technical methods.

Discussion. In the interpretation of the mild lipemia produced in the schizophrenic patient by daily hypoglycemic doses of insulin, it must be kept in mind that we are dealing with an organism characterized by a hypometabolism. This is indicated by the malnourishment, low body weight, low oxygen consumption rate, and low blood pressure found in schizophrenia (Hoskins[8]). The schizophrenic patient is also characterized by his inefficient homeostatic mechanisms. Because of these abnormal factors, a patient may not be able to maintain his optimum blood lipid level.

Insulin may have, as one of its functions, the ability to control the type of foodstuffs burned, giving preference to the burning of carbohydrate. In the severely diabetic, the high blood lipids may indicate that the subject is using more fat for energy because of the inability of the organism to burn adequate amounts of carbohydrate. Treatment of the diabetic with insulin lowers the blood lipid coincident with the improvement in carbohydrate metabolism (Joslin[10]). Macleod[13] found that insulin decreases the lipemia of diabetic dogs. Wertheimer[23] showed that insulin prevents the lipemia of phlorizin poisoning and causes phlorizin lipemia to disappear. Shih-Hoa and Mills[21] found that insulin decreases blood lipids in the lipemia of nephrosis. Thus there is no reasonable doubt that insulin lowers an abnormally high blood lipid level. This effect is probably due to the decreased oxidation of fat coincident with the improvement in carbohydrate metabolism.

In contrast to the lowering effect of insulin on a high blood lipid level, we find a raised level with prolonged administration in the schizophrenic subject. It is possible that the continued administration of large amounts of insulin has sensitized the anti-insulin mechanisms of the body which are under the control of the adrenal and pituitary glands. This has been indicated by the finding of Looney and Cameron[11] of a reduced sugar tolerance in the schizophrenic subject treated with insulin. It is possible that the stimulation of the pituitary has caused an increased supply of the fat hormone and therefore a greater utilization of fat.

That the insulin treatment has some effect on the nutritional state of the subjects is indicated by the improved appetite and the increasing body weight of the subjects during the course of the treatment. The daily depletion of carbohydrate stores by the insulin reaction may be the stimulus for the increased food intake. The resulting plethora of food may operate to raise the blood fats above the pre-treatment level. Bloor[1c] has shown that the blood lipid level in animals parallels the amount of fat in the diet. Man and Gildea[14] found that inanition tends to cause a fall in both cholesterol and phospholipid in plasma and that improvement in nutrition raises these constituents to normal levels. Although the initial rise of blood lipids was coincident with the initial rise in body weight, the fact that the subsequent changes in body weight were not accompanied by corresponding changes in blood lipids signifies the operation of some other variable factors.

The maintenance of an elevated blood lipid level during and after cessation of the insulin treatment in those cases which improve mentally under the treatment suggests that the blood lipids may serve as an index of the mental state of the patients. The rise in blood lipid may signify an improvement in the general metabolism of the patient and coincides with the improvement in mental state. This tendency of the blood lipids to rise coincident with the improvement in mental state indicates that the initial blood lipid level of the schizophrenic is below his optimum. If this is found to be true then the blood lipids should rise with improvement in mental state under other regimens of treatment or in natural remission. It must be emphasized that the blood lipid values are not outside the range of normal variation. A change of blood lipid level is significant only when the level for a given patient is compared before and after treatment and remission. One could not predict the mental status of a patient by comparing his blood lipid level with that of a normal group.

The schizophrenic process may be conceived as due to an interference with the normal oxidative reactions of the cells of the brain. The cells there become clogged with metabolites, among which the lipids may be a primary substance. The action of insulin in improving the clinical condition of the schizophrenic patient may be postulated as being brought about by an increase in the effectiveness of the oxidative mechanisms. This would result in an improvement in the metabolism of the lipids and necessitate a greater transportation of fats by the blood stream. The actual fat of the blood is undoubtedly a metabolite—a substance in process of utilization either by combustion, transformation, or storage. Phospholipid and cholesterol in the blood may function either as aids in the transport of fat or as fat metabolites. In either case it would be expected that their level would be higher when much fat is passing through the blood on the way to the tissues to be burned than where there was little. If one assumes that the postabsorptive level of blood lipids is a measure of the rate of utilization of fats, then the elevated blood lipids of the improved patients would signify an increased utilization of fat. Recent studies from this laboratory seem to indicate that the brains of schizophrenic subjects have a lower content of phospholipid than normal subjects and this might possibly furnish an explanation for the oxidative failure of lipid metabolism in the brain cells postulated above.

Summary. 1. In 5 schizophrenic patients who showed a good remission during the insulin hypoglycemic treatment, a significant rise in whole blood phospholipid, total cholesterol, and total lipid occurred.

2. In 9 of 11 patients who did not improve during the treatment, a mild lipemia occurred during the early weeks of treatment, followed by random variations about the initial pre-medication mean.

3. Insulin did not significantly affect the postabsorptive level of the blood lipids.

Grateful acknowledgment is made to Eli Lilly & Co. for liberal supplies of insulin.

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HIGH DOSAGE ATROPINE THERAPY IN CHRONIC ENCEPHALITIC PARKINSONISM.

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Our casual experience with high dosage atropine treatment of postencephalitic parkinsonism on this neurologic service was so superior to that which we had with various other treatments that we decided to study a series of cases more carefully. This led to a search of the literature on the subject, at which time we were able to find but two references in English, although one more (Hall[19b]) has since appeared.

Of these 30 patients studied, 21 were chronic encephalitics of the parkinsonian type and 9 parkinsonian cases of arteriosclerotic leutic, traumatic or doubtful etiology. One case of multiple sclerosis was included as a check. Since the study began, we have used the therapy on 17 more postencephalitic cases with equally encouraging results.

The age distribution ranged from 20 to 60; the duration of the symptoms averaged 10 years, the shortest being 3 and the longest 23.

Method. The method used was essentially that of Kleemann and Roemer with certain modifications adapted to the conditions under which we worked. We employed a 0.5% solution of atropine sulphate which was freshly prepared every second day because of its deteriorating qualities and consequent loss of efficacy. In the beginning we administered 5 drops 3 times daily and increased the dose by 1 drop each dose. Our experience with toxic signs soon taught us to begin with 1 drop 3 times a day and to increase the dose by 1 drop every second day and we have found this method to be the most satisfactory.

Once the dosage is reached at which a maximum amount of improvement has occurred, capsules or tablets containing the appropriate dosage are substituted for the drops. This is much more convenient for self-medication of ambulant cases. It also insures stability. The use of such tablets or capsules during the preliminary period of trial before optimum dose for each patient is reached is impractical, since it does not permit sufficient variation in dosage.

A few comments are in order regarding the daily distribution of the dose. An even distribution of the 3 daily doses over the 24-hour period is desirable. Due to ward routine our medication was given every 3 hours from 9 A.M. to 5 P.M. Because of this spacing the patients tended to become "de-atropinized" during the night with consequent evidence of overdosage after the morning medication. Therefore it seems advisable to maintain wherever possible an even distribution of the dose.

The incidence and nature of the toxic signs which appeared in our series of cases during the period in which they were being stabilized at their appropriate dosages is given below. Many of these signs were only transitory but they are all included.

Table 1.—Toxic Symptoms.

	Encephalitics.	Non-encephalitics.
Dryness	19	5
Paralysis of accomodation	18	1
Tachycardia	5	1
Weight loss	3	2
Urinary difficulty	4	2
Diarrhea	1	6
Constipation	2	1
Abdominal distention and hiccoughing	2	7
Nausea and vomiting	9	6
Dizziness and light-headedness	15	5
Hallucinations	6	2
Forgetfulness and confusion	11	2
Twitching of legs	1	0
Lethargy and weakness	11	6
Flushing of face	11	2

As will be noted, dryness of the mouth occurred in nearly all the postencephalitic cases. The only exceptions in our series were those which had not reached their maximum tolerance at the time this paper was prepared, as shown by the fact that their pupils were not dilated and responded to light. Dryness of the mouth is usually the earliest of the toxic signs. It is not an indication for withdrawal and the patient should be encouraged to disregard it. It may be greatly alleviated by giving chewing gum, sour candy balls, prunes, and so forth, to stimulate salivation.

Paralysis of accommodation occurred in all our postencephalitic cases excepting the 2 mentioned above and a few others in the non-encephalitic group who never received very high dosage. This sign usually occurs early in the treatment and follows shortly after dryness of the mouth. It is not an indication for withdrawal and the patient should be encouraged to tolerate it until stabilization of dosage has occurred when it easily may be overcome by proper lenses.

The next most frequent toxic sign among our patients was that of dizziness and light-headedness. Almost as frequent were lethargy and weakness. In general, these signs are more serious than dryness of the mouth and visual symptoms. In the majority of cases in which dizziness and light-headedness or "dopeyness," as the patients usually termed it, or weakness and lethargy developed, they were overcome by the simple expedient of maintaining the dosage at the level at which they occurred, for a few days, or by decreasing the dose by 1 or 2 drops, maintaining at this level for 2 or 3 days and then gradually increasing as usual. It is worthy of note that the toxic signs just mentioned as well as all others occurred with considerably greater frequency before we had changed out technique of administration—by increasing the dose more slowly. It is important to differentiate these transient signs which occur during the increase of dosage from the lethargy, anorexia, and loss of drive which supervene when actual overdosage has taken place. These signs of overdosage usually occur in conjunction with the marked aggravation of the original parkinsonian symptoms which previously had been relieved. In the case of overdosage, gradual reduction until the signs are relieved is indicated. Never abruptly withdraw the atropine. This is very important.

Flushing of the face was another frequent toxic sign. However, we feel that this was in great part due to the uneven distribution of the doses during the day, as it occurred most frequently either in the morning after the first dose (too rapid atropinization after a long period of withdrawal during the night), or shortly after the mid-day dose (cumulative effect of the morning and mid-day dose). In several very marked cases we arranged to have the night dose given at a much later hour, with practical disappearance of the flushing. A more even distribution of the medication would practically eliminate this sign.

Nausea and vomiting, accompanied by abdominal distention and in some cases hiccoughing was fairly common among our patients, particularly during the preliminary period of trial. It was particularly common among those patients who were not encephalitics. This condition was treated with gastric lavages, enemas, rectal tube and prostigmin, as well as intravenous fluids if necessary. In general, the treatment is that of postoperative distention. Later, having changed our plan of medication from daily increase to every other day, we met with these signs much less frequently. Furthermore, with careful observation, if the atropine is reduced at the first sign of abdominal distress, these signs were practically eliminated.

Diarrhea and constipation were relatively rare among our cases. Constipation appeared in only 2 encephalitic cases and in both it was only transient and was overcome easily with mineral oil; diarrhea occurred in only 1 encephalitic case as a terminal sign. Otherwise it occurred in 6 of our 9 non-encephalitics when the dosage was increased above a few minims. (We were never able to overcome this sign in the non-encephalitics, except by reducing to a very low dosage and maintaining it at that level.)

A very annoying but not at all serious toxic sign which occurred quite frequently (in over one-third of the cases) was that of transient confusion and forgetfulness. Particularly annoying was the fact that 2 or 3 patients would occasionally forget that they had received their morning medication and would bother the nurses for it. However, these episodes were transitory, and only in a few instances necessitated reduction or maintenance.

Hallucinations occurred in 6 of our encephalitic patients and in 2 arteriosclerotic parkinsons. They were usually transient and occurred most frequently after the morning dose. In the main, they were overcome by slight reduction for a short period of time. A number of the patients realized the hallucinatory nature of their symptoms, but could not control them. Transitory somnambulism occurred in 1 case.

Episodes of tachycardia occurred in 6 of our patients, but were neither marked nor of long duration. They occurred most frequently after the morning dose. Subjectively only 1 patient (R. B.) complained of this to any extent.

Difficulty in starting the urinary stream occurred in 4 cases. In 3 this was an early sign and was overcome without variation in the routine of administration. In the fourth case (H. F.), it appeared as a terminal sign, complicated by the fact that this patient had a large scrotal abscess and cystitis, so that the direct connection between the atropine and the urinary difficulties was not definite.

Twitching of the legs occurred in 1 patient (G. M.). It was his only toxic sign besides dryness of mouth and paralysis of accommodation. This twitching occurred with remarkable regularity whenever the dosage was increased above 13 drops. This patient has improved greatly on this dosage, and is being maintained with great satisfaction thereon.

Loss of weight was not marked in any case except in the terminal stages of the patient mentioned below (H. F.). Check on the weights of the patients over a 2-month period showed a light general increase. In the 4 cases in which loss did occur, it was merely a matter of 2 or 3 pounds, and might be accounted for by the increase in activity on the part of the patients. It is interesting to note that the appetites of the great majority of the patients improved remarkably under atropine therapy.

Profuse perspiration occurred in 3 patients, and may be controlled (just as flushing of the face) by more careful spacing of the daily doses and with slower increase. Our patients, although annoyed by this symptom, have accepted it because of the other improvements. It should be borne in mind that profuse perspiration may be a sign of overdosage, in conjunction with loss of drive, aggravation of parkinsonian symptoms, and so forth. But one of our patients showed skin eruptions.*

The establishment of the optimal dose for each case is a difficult problem and one which must be strictly individualized. Our experience showed no relationship to the length of time which elapsed since the onset of the parkinsonian symptoms (contrary to the experience of Roemer, who states that the further away from the acute encephalitic episode the better the response, and of Marinesco and Facon, who found that recent cases reacted better than old cases which had previous therapy). In general, the optimal dose may be established in the manner described by Roemer and Kleemann, *i. e.*, when the maximum is reached, it is maintained and then reduced slowly to a point just above that at which the parkinsonian signs appear. However, we have found that the length of time necessary to establish tolerance was very variable. Due to the difficulties mentioned above, there were occasional lapses in the treatment which probably added to our stabilization time. In general, approximately 2 to 4 months are necessary to establish the optimal dose. In some few cases (*e. g.*, G. M.), toxic signs appeared at a very low dosage and reduction of a few minims gave maximum subjective and objective improvement. In others, toxic signs did not appear until very high doses had been reached, and then considerable reduction was necessary until the optimal dose was reached. Still other cases developed toxic signs at a certain definite level, and were maintained at that level or slightly below it at what appeared to be the stabilization point. After a few weeks at this dosage, the tolerance apparently increased, and the symptoms reappeared, necessitating further increase and readjustment. In 1 or 2 cases this has been so pronounced that, even after a number of months, stabilization has not yet been attained. However, this is not usual. Most cases reach a certain maximum and may then be reduced to the optimal dose with little difficulty. It has been our experience that the optimal dose is remarkably exact. Variations of 1 or 2 drops (either increase or decrease) were immediately detected by the patients and could often be confirmed by objective signs (*e. g.*, G. M., who was stabilized on 13 drops and invariably detected any variation).

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* During a spell of extremely hot weather, practically all of our atropine patients developed very high temperatures accompanied by rapid pulse and hot, dry skin. A few developed confusion and delirium. In all there was a complete lack of disagreeable subjective symptoms. The treatment was not interrupted.

The maximum stabilization dose reached by any of our patients was drops 70 t.i.d. (an equivalent of 17.5 mg. or 0.35 gr. t.i.d.), the minimum was drops 10 or an equivalent of 2.5 mg. or 0.05 gr. One patient (A. A.) was temporarily stabilized at drops 7 t.i.d. for 2 weeks, due to the appearance of toxic signs. He showed signs of lowered tolerance after that, but signed a release from the hospital before further work was done. The average dose for all our patients was drops 32 t.i.d. an equivalent of 8 mg. or 0.13 gr.

The distribution of the dosages was as follows: from 0–5 mg. t.i.d., 9 patients; 5–10 mg. t.i.d., 5 patients; 10–20 mg. t.i.d., 7 patients.

In common with the experience of most observers, we were not able to reach the enormous dosages attained by Roemer and Kleemann. None of our patients exceeded 17.5 mg. t.i.d.* However, average distribution of dosages agrees essentially with that of the original observers, with a slight preponderance in the lowest group (from 5–10 mg. t.i.d.).

Analysis of Results. The accompanying table shows graphically the results obtained with atropine therapy over the period during which this therapy has been applied.

TABLE 2.—INFLUENCE OF MEDICATION ON SYMPTOMS.

(Total number of patients 21.)

Postencephalitics.

	Salivation.		Rigidity.		Tremor.		Assoc. move.		Speech.		Pulsion.		Facies.		Oculogyric.	
Very marked	15	0	19	0	11	1	19	0	14	0	8	0	19	0	2	0
Marked	2	0	1	4	5	2	1	8	5	2	3	1	2	6	0	0
Moderate	5	2	1	10	3	8	1	7	2	9	2	3	0	5	1	0
Slight	1	5	0	5	2	7	0	4	0	6	11	4	0	8	0	1
Absent	0	14	0	2	0	3	0	2	0	4	7	13	0	1	18	20

Non-encephalitics.

	Salivation.		Rigidity.		Tremor.		Assoc. move.		Speech.		Pulsion.		Facies.		Oculogyric.	
Very marked	2	0	7	5	4	3	7	6	6	5	0	0	5	3	0	0
Marked	0	0	1	3	3	3	1	3	1	2	0	0	3	4	0	0
Moderate	1	2	0	0	2	3	0	0	1	1	0	0	0	1	0	0
Slight	1	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
Absent	5	6	1	1	0	0	1	0	0	0	0	0	0	0	0	0

The figures in the left-hand column under each symptom represent the number of patients and degree of severity of the symptoms before treatment; the figures on the right the same at the close of treatment.

The objection may be raised that this method of judgment is purely subjective, and therefore does not give a proper picture of the cases. However, such things as the ability to speak, the ability to dress and care for one's self. the movements of the hand and wrist on opening and closing the fingers, and the ability to drink fluids without spilling them appear to us to be sufficiently objective. Naturally, this could not be shown in detail in a table.

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* The maximum dose of atropine required before stabilization was reached as reported in our series was 70 drops t.i.d. Since finishing the paper, one case has been carried to 110 drops t.i.d. with gradual and steady improvement and stabilization has not yet been reached.

A brief analysis of the results obtained in our cases follows:

Salivation. Fifteen of the 21 patients drooled to a very marked extent before therapy was begun, and the remaining 6 showed this sign to a slighter degree. Following therapy, salivation had completely disappeared in 14 of the patients, was very mild in 5 others, and the 2 who still salivated moderately had not yet reached higher doses and were not stabilized. Salivation was not marked among the non-encephalitic cases, and showed very little change with medication.

Rigidity, Disturbances in Associated Movements, and Masked Facies. These three symptoms may be treated together, as they more or less complement each other. In the 21 patients, 19 were very rigid before treatment. One of them was markedly so, and the last showed only moderate rigidity. Following treatment only 2 of the patients were judged to be normal and to have normal associated movements; 15 others showed slighter degrees of rigidity and 4 were still markedly rigid, but none showed as much rigidity as before the treatment. The associated movements did not completely parallel rigidity, as only 11 showed fairly marked improvement, while in the remaining 8 the associated movements were poor. Masked facies showed practically the same numerical distribution before therapy, but improved to a less extent than the other two symptoms. In only 1 patient there was no change at all, 11 showed moderate or masked-like facies, and in 8 it was felt that there was good expression in the face, as judged by the ability to smile, laugh, and respond to emotional stimuli. As can readily be seen the non-encephalitics showed only very slight changes under therapy.

Speech. This symptom was one of the most dramatic of all in its improvement. Before therapy was instituted 14 of the patients had such marked speech difficulties that they were practically unintelligible; 5 could be understood with difficulty and only 2 showed moderate speech impairment. Following therapy, 4 of the patients were able to speak with no difficulties whatsoever, 6 had occasional difficulties, 9 had definite speech disturbances although they could be understood. The remaining 2 could be understood with difficulty, and were 2 of those who had been completely unable to utter a word before. Of the non-encephalitics, only 1 patient showed some slight improvement in his speech, the others were unchanged.

Pulsion. This was very marked in 8 of our patients, marked in 3, moderate in 2, slight in 1 and absent in 7. These were those patients who were bedridden. Six of our ambulant patients showed no signs of pulsion after treatment, 4 had only a very slight degree of pulsion, and the other 4 still showed moderate signs.

Oculogyric Crises. These were present in only 3 of our cases, in 2 to a very marked degree, and in the other only slightly. They disappeared in 2 cases, and remained present to a slight degree only in 1 of the more severe cases.

Severe and Constant Cramp-like Jaw Movements. These which made life a torture to 1 patient were so modified as to be almost unnoticeable.

Summary. 1. As insufficient attention has been paid to high dosage atropine therapy and the technique of administering the same in cases of chronic encephalitic parkinsonism in the English and American literature, we have reported our preliminary experience with this therapy and have given an extensive bibliography.

2. Thirty cases, of which 21 were of encephalitic origin and the remaining 9 of other etiology, served as the material for our study. Since this study was commenced, 17 more cases have been added to our experience with equally good results. The period of this study was approximately 9 months.

3. A detailed analysis of the difficulties, toxic signs, and beneficial results obtained with this method is given.

4. Our experience, in accordance with those of European investigators, shows that this method is far superior to the various other methods we had used in such cases.

5. The results obtained with non-encephalitic cases have led us to feel that this method may serve almost as a differential diagnostic point.

Case Histories. Case 1.—W. A., aged 28, white male, had encephalitis in 1932 followed shortly by tremors of all extremities associated with rigidity, oculogyric crises, and difficulty in speaking. Physical examination on admission was essentially negative. Typical parkinsonian symptomatology. Previous to atropine therapy patient had received hyoscine (gr. 1/100), fever therapy, and so forth, with no change in status. Patient started on atropine therapy on 10/7/36. Dosage was increased steadily without toxic signs until reaching min. 71 when he developed hallucinations and was completely disorientated. Dosage slowly reduced and now stabilized on min. 53 with maximum subjective and objective improvement. Oculogyric crises and speech difficulty have entirely disappeared and other symptoms are so greatly improved that he is very comfortable and seeks his discharge.

Case 2.—M. R., aged 38, white male, had sleeping sickness at the age of 20, followed by tremors and rigidities which gradually increased in severity, so that at the age of 27 he was forced to leave his position as salesman. Was admitted to hospital in 1933 with typical parkinsonian signs, rigidities predominating and tremors slightly marked. Speech difficulties were so marked that the patient appeared almost anarthric at times. He received hyoscine in usual doses and intravenous typhoid injections with no change in status. On 10/3/36 patient was started on atropine therapy, but was extremely uncoöperative and often refused to take medication. On 11/6/36 it was noted that patient was going downhill—his rigidities were more severe, the difficulties in speech were marked and he claimed that he could not chew his food. However, atropine was continued with little change in status until 1/25/37 (when patient was receiving min. 27). He complained of marked dizziness and grogginess. Since the atropine had not improved any of his symptoms except salivation it was decided to discontinue the therapy, much to the relief of the patient. Two days later the patient was confined to bed, complained of marked weakness and increasing rigidity, and requested resumption of the atropine. The following day the patient was again started on min. 10 and gradually increased to min. 46. This time the patient coöperated very willingly. He improved subjectively, feeling stronger and more cheerful and lively. Objectively his speech and gait improved considerably, his facial expression lost its masklike character and the rigidities were much improved. The only toxic episode was a transient period of dizziness and nausea. Dosage was increased gradually to min. 53 when the patient complained of tiredness, and weakness in the legs. Dosage reduced to min. 50, and patient was stabilized at this dose with improvement as noted above. Patient is very active on ward and has been gaining considerable weight.

CASE 3.—W. S., aged 50, white male, admitted to hospital on 1/25/30. Onset of tremor and rigidity in 1923 following sleeping sickness of 4 months' duration. Gradual progressive increase of symptoms which necessitated hospitalization. Soon after admission patient became non-ambulant, practically confined to bed, only up in wheel chair at times. Findings on admission were those of a typical parkinsonism—marked facies, greasy skin, excessive salivation, extreme difficulty in speaking, fine tremor of the right hand, normal reflexes, and so forth. Laboratory studies entirely negative. The usual therapy, hyoscine, atropine in usual doses, stramonium, fever therapy, and so forth, were tried with no success. About 6 weeks after atropine therapy (dosage of min. 20 t.i.d.) patient was able to hold his body straighter and to walk a few steps unsupported. The improvement continued for 3 months (dosage of min. 42) after which patient became weak, felt nauseous, lost his appetite, and developed marked flushing of the face. The dosage was gradually reduced over a period of several weeks to min. 39, at which dose the toxic signs disappeared. After a few days at this dosage, it was gradually increased without the appearance of toxic signs. The objective improvement was as follows: speech was clear and understandable, opening and closing of fists showed normal associated movements (patient states: "it used to take me a half hour to open one hand, now it takes me a second!"). The patient was ambulant and able to walk around the ward unassisted, feed himself, dress himself. Subjectively the patient was cheerful and coöperative, became interested in ward activities and planned to go home. By the end of May, 1937, the patient was walking around the ward freely and appeared almost completely free of his original symptoms. At this time he was receiving min. 73, t.i.d. On 6/15/37, at min. 80 t.i.d. the patient developed toxic signs as follows: weakness, inability to walk, increased tremors, a slightly cachectic appearance. Gradual reduction led to stabilization at min. 70, with maximum subjective and objective improvement. He felt fine at that dose and has been discharged for follow-up in the clinic.

CASE 4.—S. K., aged 36, white male, admitted to hospital on 5/15/36. History of encephalitis with diplopia and "sleeping" for 1 month in 1921. In 1927, the patient developed difficulty in swallowing, excessive salivation, with tendency to cramplike opening of the mouth accompanied by cramplike shutting of the eyes. The findings on admission were as follows: masklike facies with the above cramplike movements of jaw and eyes, pupils unequal, slight left central facial, cogwheel phenomenon in upper extremities, bilateral Babinskis, no tremors, generalized rigidity. Laboratory studies entirely negative. The usual parkinsonian therapy gave no relief. Patient was put on high dosage atropine therapy on 10/3/36. Stabilized at min. 30 for about 7 weeks with loss of toxic signs and recovery from above mentioned symptoms.

CASE 5.—H. F., aged 56, white male, readmitted to hospital on 5/13/36. Influenza in 1925, followed 2 years later by masking of the face, and loss of associated movements in the left arm, which shortly thereafter developed a mild tremor. Since 1934 there has been progressively increasing difficulty in walking, accompanied by difficulty in speech and excessive salivation. Examination on admission showed essentially the findings as mentioned above, plus old varicose ulcers of both legs and a chronic osteomyelitis of the right ankle. Laboratory studies completely negative. Previous treatment included hyoscine and stramonium with no effect. On 10/4/36 the patient was started on high dosage atropine therapy. At dosage of min. 27 the patient showed marked improvement which increased with the increasing dosage so that his tremors had practically disappeared, salivation was completely absent, his speech was clear and distinct, he was able to walk around with ease. Subjectively the patient stated that he "felt fine, better than ever before I took sick."

CASE 6.—G. M., aged 25, white female, admitted to hospital on December 27, 1929, with a history of influenza in 1918. In 1922, the patient noticed stiffness of her muscles and slowness of movements. In 1929, she noticed tremors of both arms which gradually increased so that patient had to be hospitalized. Examination on admission revealed masked facies with greasy skin, marked propulsive gait, tremors of all extremities, excessive salivation, cogwheel phenomenon in both arms and eyes, normal reflexes. Speech was slow and monotonous and difficult to understand. Laboratory studies completely negative. The usual therapy was of no avail. The patient was practically confined to her wheel-chair because of her propulsive gait, and was unable to help herself because of her tremor. On 1/28/37 she was put on high dosage atropine therapy with gradual increase until min. 15 t.i.d. was reached. At this time the patient complained of twitchings of the legs, most marked at night and in the late afternoon. The dosage was increased to min. 20, then slowly decreased to min. 13 t.i.d., at which dose the patient no longer showed twitchings of the legs. At this dose she showed the following improvements: she was able to feed herself, able to embroider, her speech was clearer, more understandable and rapid, she was able to stand up straighter, but there was still slight propulsion in her gait. Subjectively, the patient changed from the "ward grouch" to a pleasant, coöperative, interested member. She never tired of stating that she "never felt better in her life." The patient has been stabilized at min. 13, since March, 1937, with no complaints whatsoever. Several attempts to increase her above min. 13 have resulted in twitchings of the legs, so that we have considered her stabilized at this dose.

CASE 7.—I. L., aged 22, white female, admitted to hospital on 4/23/32, unable to give any history. History obtained from family as follows: sleeping sickness in 1922 at Bellevue Hospital for 3 months. Since that time gradually progressing tremors, rigidities, speech difficulties and complete inability to walk. Various forms of therapy at different hospitals were completely unsuccessful. Examination on admission showed typical parkinsonian symptoms with marked tremors and rigidities. Laboratory studies essentially negative. The patient was completely bedridden. On 1/28/37 she was started on high dosage atropine therapy. At min. 12 t.i.d. she became nauseous and vomited, and appeared disorientated. The dosage was maintained for a few days, and then increased again when the toxic signs disappeared, only to reappear at min. 20 t.i.d. The only improvement noted was that salivation had decreased to a certain extent. The dosage has been increased gradually with no recurrence of toxic signs until at the time of writing the patient was receiving 49 min. t.i.d. with no improvement except for the salivation, and as the nurse on the ward stated "perhaps a better ability to swear at us, but nothing else."

Case 8.—L. D., aged 62, white female, admitted to hospital on 9/28/35 on the surgical service with diagnosis of phlebitis of the left leg. Tremors of both hands were noted, with the history that it had started 2 years before admission. Otherwise the history was negative for encephalitis, influenza, and so forth. Neurologic examination following transfer showed markedly arteriosclerotic fundal vessels, irregular pupils, cogwheel phenomenon of the eyes, slightly greasy facies, tremor of the tongue, hands, and slightly of the legs. Generalized hyperreflexia and bilateral Babinski. The diagnosis of parkinsonism on an arteriosclerotic basis was made. Therapy, as usual, did not change her condition any. On 1/28/37 the patient was put on atropine therapy. She reached the dosage of min. 12 with no toxic signs, but at this dose began vomiting. There was absolutely no sign of improvement. Gradual reduction was of no avail and the patient continued to vomit as long as medication was continued and after a short while therapy was discontinued.

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Appendix on the So-called Bulgarian Cure.*

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* There is a very extensive literature on the so-called Bulgarian cure, but in order not to burden the bibliography and because of the opinions expressed in the text, we give here only a few references.

STUDIES OF THE BLOOD PROTEINS IN DELIRIUM TREMENS.

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There is much evidence that the polyneuritic, pellagrous and cardiovascular complications which appear in the course of some cases of chronic alcoholism are due to nutritional deficiencies and not to the "toxic" effects of alcohol (Shattuck,[12] Wechsler,[15] Minot, Strauss and Cobb,[8] Jolliffe, Colbert and Joffe,[6] Spies and DeWolf,[14] Weiss and Wilkins[16]). Whether alterations in nutrition contribute to the onset of the more acute alcoholic disorder, delirium tremens, is, however, not established. It is generally assumed that a low intake of food, fear and loss of sleep contribute to the development of the delirium. Chemical studies which have been made on patients suffering from delirium tremens fail to throw much light on their nutritional state.

This paper presents the results of observations of the total serum protein, serum albumin, and serum globulin in 24 male patients whose ages varied between 25 and 49 years. All gave a history of excessive drinking which was increased in amount shortly before the onset of the delirium. Upon arrival at the hospital they exhibited confusion, disorientation, visual and sometimes auditory hallucinations. Except for 6 patients with mild respiratory infections, the subjects were free from pulmonary complications, head injury, kidney disease and gross clinical evidence of liver disorders, such as jaundice or palpable hepatic enlargement. Edema was not observed in any of the cases. Specimens of blood were obtained without stasis from an antecubital vein before the patient was allowed to have food, fluid or medication in any form, and again after the features of the acute psychosis had subsided. The interval between the first and second determinations varied from 4 to 10 days. Dietary histories were obtained from the relatives of the patients and from the patients themselves as soon as they were able to coöperate.

The total protein and albumin values were determined from the serum by a combination of the methods of Howe,[4] Wu,[18] and Koch and McMeekin.[7] As a check on the procedure used in the protein studies, determinations were made on 6 healthy male members of the medical staff whose ages were between 22 and 36 years. The total protein values of these subjects ranged between 5.8 and 6.4 gm. % (average 6.1 gm. %). The albumin component ranged between 4 and 4.8 gm. % (average 4.36 gm. %). Globulin values ranged between 1.6 and 1.9 gm. % (average 1.76 gm. %).

Table 1 shows the values for the protein determinations on admission and at the time of discharge.

TABLE 1.—TOTAL SERUM PROTEIN, SERUM ALBUMIN, AND SERUM GLOBULIN ON ADMISSION AND AT THE TIME OF DISCHARGE IN 24 CASES OF DELIRIUM TREMENS.

	Values on admission.			Values on discharge.		
Number.	Total protein, gm. %.	Albumin, gm. %.	Globulin, gm. %.	Total protein, gm. %.	Albumin, gm. %.	Globulin, gm. %.
1 . . .	4.5	2.5	2.0	4.7	3.1	1.6
2 . . .	4.7	2.2	2.5	4.6	2.3	2.3
3 . . .	4.9	2.9	2.0	6 2	3.7	2.5
4 . . .	4.9	3.7	1.2	4.9	2.5	2.4
5 . . .	5.0	3.1	1.9	5 5	3.2	2.3
6 . . .	5.4	2.4	3.0	4.5	2.0	2.5
7 . . .	5.4	2.8	2.6	6.1	3.6	2.5
8 . . .	5.4	3.1	2.3	5.2	3.0	2.2
9 . . .	5.5	3.4	2.1	5.0	3.0	2.0
10 . . .	5.6	3.0	2.6	5.7	3.0	2.7
11 . . .	5.7	3.3	2.4	7.0	4.4	2.6
12 . .	5.7	3.6	2.1	6.7	3.6	3.1
13 . . .	5.8	4.4	1.4	6.1	3.7	2.4
14 . . .	6.0	4.2	1.8	5.0	3.5	1.5
15 . . .	6.0	3.0	3.0	5.9	3.0	2.9
16 . .	6.1	5.0	1.1	6.7	5.4	1.3
17 . . .	6.3	4.6	1.7	4.5	3.1	1.4
18 . . .	6.5	3.4	3.1	6 6	3.4	3.2
19 . . .	6.6	3.9	2.7	5.4	3.0	2.4
20 . . .	6.8	3.4	3.4	6.0	2.9	3.1
21 . . .	6.0	4.4	2.5	6.2	3.9	2.3
22 . . .	7.3	3.9	3.4	6.4	3.4	3.0
23 . . .	7.6	3.3	4.3	6.2	2.8	3.4
24 . . .	8.3	4.7	3.6	6.5	2.6	3.9

In 18 of the 24 patients, upon admission to the hospital, the serum albumin was below the lower limit of the normal range (4 gm. per 100 cc.), and in 22 of the 24 patients it was below this value upon discharge from the hospital in spite of the fact that all received high caloric and relatively high protein intakes during their hospital stay.

In attempting to evaluate the food intake of these patients before the onset of their delirium, we encountered a difficulty already known to those who are familiar with cases of delirium tremens. All of the patients stated that they ate "poorly" before the onset of the psychosis, but when one sought detailed information concerning the type and amount of food that they consumed, a variety of data was received. Some patients stated that they ate "nothing for several days" before the delirium. Others stated that they ate "only one meal a day." One man took "only soup when drinking heavily." Another could not eat for 7 days before his psychosis appeared. A few patients who were sent to the hospital by the police tended to minimize the amount of their drinking for one reason or another and utilized whatever neglect of food there was to further their contention that they were light drinkers—that if they had eaten properly they would have avoided the delirium tremens. One might be inclined to ignore the explanations of this special lot of cases if it were not for the fact that all other cases of delirium tremens related a similar story with regard to their food intake. It is significant that all of our 24 cases, as well as many cases not included in the group, gave a history of an inadequate diet before the onset of the delirium.

Comment. It is possible that dietary deficiency is responsible for the reduction in the serum albumin. That malnutrition results in a hypoproteinemia in which the albumin is chiefly affected is well known. However, granting that there is dietary deficiency in delirium tremens, this may not be entirely responsible for the reduction in the albumin. It is known that the liver undergoes pathologic changes in some cases of chronic alcoholism. Since 1918, when Whipple[6] and his associates noted that albumin and globulin were more slowly restored after plasmapheresis by animals with injured livers, many investigators have contributed data showing that severe liver damage in man is accompanied by a reduction in the albumin of the plasma (Wiener and Wiener,[17] Myers and Keefer,[9] Peters and Eisenman,[10] Snell,[13] Foley,[3] and others). Opinions differ concerning the true rôle that the liver plays in the reduction of the albumin. Here it suffices to state that some observers (Wiener and Wiener[17] and others) have attributed the reduction to a deficiency of the albumin-forming properties of the liver, believing that this organ is the site of albumin production. Others (Peters and Eisenman[10] and others) contend that the reduction in albumin is the effect of the serious hepatic insufficiency upon the general nutrition, that malnutrition is the chief factor responsible for the low albumin. Concerning this unsettled question the cases of our series are of interest only insofar as that no signs of liver damage could be demonstrated by means of jaundice or enlarged and tender liver in any of the cases. None of the cases showed symptoms usually included in the clinical picture of delirium tremens longer than 4 days. All cases were discharged as recovered from the acute features of their attack of delirium tremens within a period of 10 days. Specific studies on the blood and urine which might enable one to detect evidences of a disturbance of liver function unrecognizable otherwise were not done. Increase of bilirubin in the blood and/or urobilinogen in the urine of patients suffering from delirium tremens has been reported by Pohlisch,[11] Büchler,[2] Binswanger,[1] and others.

It should be stated that some of the patients referred to in this report left the hospital as soon as the acute mental features of their disorder subsided. Although the psychosis of every patient had disappeared at the time of discharge, data here presented indicate that the serum albumin of some cases had not returned to normal. The observation that the serum albumin value of 12 cases was lower at the time of discharge than it was on admission might be explained by a restoration of plasma volume to a higher level, since some of the patients seemed dehydrated at the time of admission.

Summary. 1. The total serum protein, serum albumin, and serum globulin of 24 patients with delirium tremens were determined on admission to the hospital and after the acute delirious phase of the psychosis had subsided.

2. The serum albumin of 18 cases was below 4 gm. % per 100 cc. of blood on admission. On discharge the serum albumin of 22 cases was below 4 gm. % per 100 cc. of blood, the albumin value of 12 of these 22 cases being lower than it was on admission.

3. There was no significant alteration in the serum globulin values either on admission or at the time of discharge.

The authors are indebted to Dr. Maurice B. Strauss for his advice in connection with the performance of these observations and the preparation of the manuscript.

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BOOK REVIEWS AND NOTICES

NEUROLOGY. A Most Comprehensive and Unified View of Modern Clinical Neurology. By ROY R. GRINKER, M.D., Chairman, the Department of Neuropsychiatry of the Michael Reese Hospital, Chicago; Formerly Associate Professor of Neurology and Psychiatry, The University of Chicago. Pp. 999; 406 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1937. Price, $8.50.

THE appearance of the second edition of Neurology by Dr. Roy Grinker affords this Reviewer another opportunity to view with amazement the scope of this work, to express his pleasure at the presentation of neurology as a field of biology but in the confines of a single volume. One wonders whether succeeding editions can possibly pursue this same ambition in one book without resorting to the use of sections of finer print or without discarding much of the material which makes this treatise comprehensive.

A mere cursory survey reveals that this edition represents more than a reprinting with correction of the usual minor errors which crop up in any large book.

As before, the opening chapters are concerned with the development and structure of the nervous system which are covered adequately. The profuse use of illustrations, diagrams and tables adds to the clarity of presentation. The next general section is concerned with the physiologic structure and then the function of the several important parts of the nervous system.

However one feels that such chapters as General Pathological Considerations, Technic of Neurological Examination, Tumors of the Peripheral Nerves and Spinal Cord and Intracranial Tumors are really out of place and should be withheld to their more logical places with other diseases and pathologic conditions. In this regard one feels that the chapter on the Anatomy and Physiology of the Blood Supply might follow that on the Coverings and Interstitial Tissues and the chapter on Developmental Defects might occupy a position among the pathologic conditions corresponding to that on Embryology. These however are minor suggestions. It is obvious that the chapters on the Vegetative Nervous System, the Cerebral Cortex and those on the inflammations and infections have been subjected to heavy revisions. One notes not only the inclusion of recently established facts but also brief analyses of both sides of important controversial matters. In many cases this is accomplished by quoting authors directly.

New material on electro-encephalography, migraine, myasthenia gravis, myotonia congenita, cortico-cerebellar relations and more recent concepts of the effects of vitamin deficiencies are notable additions to the present editions.

As before, the volume is profusely illustrated with beautiful pictures and [illegible] Numerous comparative tables of symptoms and signs [illegible] of the context.

As usual the bibliography appended to each chapter is adequate and all references have been subject to revision. The index is comprehensive and is of great value since in a work of this character some repetition of material in the several sections is unavoidable.

The Reviewer again feels that this is the best single volume on General Neurology which has been produced in this country and one of the best in the English language. E. T., JR.

LEGAL MEDICINE AND TOXICOLOGY. By THOMAS A. GONZALES, M.D., Acting Chief Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine, etc.; MORGAN VANCE, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc.; and MILTON HELPERN, M.D., Assistant Medical Examiner of the City of New York, etc. With a Foreword by HARRISON S. MARTLAND, M.D., Chief Medical Examiner, Essex County (Newark), New Jersey, etc. Pp. 754; 244 illustrations. New York: D. Appleton-Century Co., Inc., 1937. Price, $10.00.

THE authors' aim "to prepare a book which would be sufficiently complete to use as a satisfactory source of reference but brief enough to serve the student as an introduction of medicolegal science" has been definitely fulfilled. Excellent judgment was used in allocating space; information necessary to the active participation of the physician in a given situation is presented in detail; police problems, etc., being mentioned briefly to indicate correlation. General legal implications are considered but finer points of law are wisely referred to a competent legal consultant.

The division of the book into two main sections, dealing with legal medicine and toxicology respectively, is orthodox. The first is more completely handled than usual as regards autopsy findings and is profusely illustrated with good photographs. Aids to decision regarding time and manner of accidental death are presented, indicating very clearly, however, the limitation of observations related thereto. The chapter on unexpected natural deaths is important; the technique and medicolegal angles of blood examination are given deserved space of 40 pages. Problems relating to sexual assault, illegitimacy, abortion and insanity are more briefly mentioned but are adequate. Toxicologic analysis is discussed separately in a section of 80 pages and should be particularly helpful to those who lack familiarity with the field. Full discussion of technique obviously could not be accomplished and, although the subject is well presented from the standpoint of postmortem examination, the procedures described usually would offer little assistance in the detection of chronic poisoning in the living. A list of pertinent references is appended to each chapter and the index is good. The Appendix, which contains condensed tables from the statistical report of the Chief Medical Examiner of the City of New York for 1935, lends definite authority to the statements and opinions of the authors.

It occurs to the Reviewer that, apart from the value of the book *per se*, it represents a serious indictment of the politically controlled, ever-changing and usually incompetent average coroner's office. Under the New York law the Chief Medical Examiner is "a doctor of medicine, and a skilled pathologist and microscopist," his assistants likewise, removable only by reason of proven incompetence or misdemeanor. Solely through such an organization, working undisturbed over a period of years, is it possible to accumulate data and experience necessary to the successful prosecution of crime and invaluable in the preparation of a book of this character. P. C.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, with 8 Collaborators. Pp. 1051; 355 illustrations and 103 tables. Eighth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $8.50.

THIS new edition of this standard textbook of physiology is the first since Macleod's death, and although only 3 years have elapsed between editions, it was found necessary to rewrite the book almost completely. This has been done by a staff of editors, some of whom took part in the previous revision, but most appear for the first time, *e. g.*, H. C. Bazett, who writes the chapter on the circulation; C. F. Schmidt, the respiration; G. R. Cowgill, the alimentary tract; M. I. Gregersen, the kidney. The advantage of such collaboration is that both text and references are up to date; this can be done only by specialists writing each in his own field. This advantage probably outweighs the disadvantages of unequal treatment of the sections and neglect of some subjects (the leukocytes are treated in 11 lines).

It should be emphasized that this book, as was true also of earlier editions, is a textbook of physiology and not as its title implies a treatise on physiology applied to medicine. There are, of course, sections on applied physiology, though these have been printed in small type, fatiguing to the Reviewer. Those readers who are chiefly interested in the application of physiology to their medical problems will find the several sections of unequal value. Thus the chapter on the alimentary canal will not be found very helpful, whereas in the chapter on respiration there are admirable discussions of such conditions as cyanosis and anoxia.

M. McC.

APPROVED LABORATORY TECHNIC. Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical, and Histological. By JOHN A. KOLMER, M.D., DR. P. H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine, Temple University; Director of the Research Institute of Cutaneous Medicine, Philadelphia, etc., and FRED BOERNER, V.M.D., Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Bacteriologist, Graduate Hospital, Philadelphia, Pa. Pp. 893; 380 illustrations and 12 colored plates. Second edition, rewritten, revised and reset. New York: D. Appleton-Century Company, Inc., 1938. Price, $8.00.

AFTER 7 years a new edition of this book appears, with 5 new chapters and 28 collaborators. These collaborators figure in all but 9 of the 38 chapters, though the nature of their collaboration is not indicated. The many new methods developed in recent years have required much rewriting, which appears to have been done carefully and well.

E. K.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Including Medicine, Surgery, Obstetrics, Gynæcology and Other Special Subjects. *Vol. 5. Endoscopy of Respiratory Tract to Goitre. Vol. 6. Gonorrhœa to Hydrotherapy.* Under the General Editorship of SIR HUMPHRY ROLLESTON, BT. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a Consultative Capacity of F. R. FRASER, M.D., F.R.C.P., G. GRAY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. ED., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F. R. S., F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Vol. 5, Pp. 683; 139 illustrations. Vol. 6, Pp. 850; 89 text illustrations and 7 plates. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, $12.00 per volume.

THIS fifth volume, continued on the lines described in earlier reviews, covers 46 subjects, ranging from Endoscopy to Goitre. Fœtus diseases, etc., in 53 pages approximates a veritable treatise on the subject. Other important topics are Enteric Fevers, Epilepsy, Fibrositis, Fungous Diseases and Gassing. One regrets that, as usual in the last named topic, the action on the hemopoietic system is apparently not appreciated. Six excellent plates and 139 text illustrations of varying merit are included.

THE 39 articles of this sixth volume necessarily include a number of blood conditions and also 10 subdivisions of heart disease. "Gonorrhea," "The Hand," "Hernia" and "Hydrotherapy" each cover more than 20 pages. However, in general, one is sharply reminded that even an encyclopedia of this size should be used as a quick, handy reference book, and not be confused with other types of medical texts that can give more adequate treatment of the topics included.

E. K.

THE PHYSICIAN'S BUSINESS. Practical and Economic Aspects of Medicine. By GEORGE D. WOLF, M.D., Attending Otolaryngologist, Sydenham Hospital; Attending Laryngologist, Riverside Hospital, New York City. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. Pp. 384; 57 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $5.00.

THIS book attempts to cover in a single volume the many problems of an economic and practical nature which confront the physician during the establishment and maintenance of medical practice. The contents, although vaguely familiar to every physician, are here organized and readily accessible, in such a way as to be of practical value. I believe that its greatest worth will be to the beginner, in the organization and conduct of his early practice. L. H.

MANUAL OF HUMAN DISSECTION. By EDWIN M. SHEARER, PH.D., Associate Professor of Anatomy, New York University College of Medicine. Pp. 321; 79 illustrations (author's original drawings). Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.25.

"IF any apology be needed for the appearance of the present Manual, it may be stated, without any wish to disparage the labors of others, that the works of this kind hitherto published seem to the author open to one or the other of two objections—either as being too systematic, and therefore not adapted for the dissecting-room, or as obscuring the more important features of Anatomy by a multiplicity of minute and variable details." (From the preface of the "Dissector" of Luther Holden, 1851.)

"The following laboratory guide to the dissection of the human body is presented in the hope that it may be found useful by those who, like the author, have come to feel that, with the serious decrease in the number of hours allotted to the subject of gross anatomy in American medical schools of recent years, the admirable but lengthy guides at present available are not entirely satisfactory." (From the preface of the subject of this review.)

If we take Corner (Clio Medica—Anatomy) at face value, "Practically all the information to be gained by the old basic method of the science, dissection of the human body, was in hand about a hundred years ago. There is very little gross anatomy in current textbooks that was not in those of Charles Bell, Henle, or Sappey." Apparently no teacher of anatomy in the intervening years has ever found a completely satisfactory method for adjusting the length of the art to the shortness of student life. The limitation of the time devoted to the course in anatomy, however, seems to be making itself acutely felt. This may be because the teacher, with wider interests, feels that he must conserve his own time by better organization of the course. Although we have had the excellent short dissector of Heisler, a few remaining copies of the short 1910 edition of Cunningham, the "Note Book" of A. Melville Paterson (1914), the outline of Emmel, the "Introduction" of Terry, the very short dissector of McCotter—to name a few, the last year has brought forth the "Method of Anatomy" by J. C. Boileau Grant and the work of our present author.

Dr. Shearer has set for himself the task of attenuating the subject of gross anatomy. He urges the student to approach dissection with the serious respect that the material demands and with a reflection upon the manner in which the right to dissect has been gained. He gives advice as to the care of instruments, and of course, his version of the indispensable instruments. There follows a strictly morphologic account of the structures as exposed by regions, and directions for their morphologic exposure. The primary purpose of the author is hereby rigorously fulfilled. It seems too bad that the student is not told how to pull upon or twist a muscle or tendon in order to bring out the contribution of the living muscle to the complexity of joint action. The mention of the functions of nerves is a slight deviation from the strictly morphologic character. Applied anatomic considerations, although extremely limited, are occasionally found. For example, the relations of inguinal hernias are discussed, but here the common use of the inferior epigastric vessels as an anatomic landmark for separating direct from indirect hernias is studiously avoided. In the preface, the author recounts and justifies certain omissions (for example, lymphatics), but no mention, neither in the preface nor in the body of the work, is made of the contents of the temporal bone. In view of the material on the orbit, on the nose, and on the larynx, this is a bit surprising. The statements about the dura are in line with the classical descriptions and do not reflect the recent studies of Popa and others. In brief, this is a topographic outline of the morphology (strictly speaking) of the human body, with directions for its exposure.

In the mechanical details of making the book, much thought has apparently been placed upon the binding, the paper, and the style of type. The spacing of the letters and the leading of the lines, together with the omission of subheadings seems unfortunate. The finished page has a monotony which renders ready reference difficult. O. B.

TEXTBOOK OF EXPERIMENTAL SURGERY. By JACOB MARKOWITZ, M.B. (TOR.), PH.D., M.S. in Experimental Surgery (Minn.), Research Associate, Department of Physiology, University of Toronto; formerly Professor of Physiology, Georgetown University School of Medicine, Washington, D. C., etc. Pp. 527; 330 illustrations. Baltimore: William Wood & Co., 1937. Price, $7.00.

THIS interesting volume is more than a textbook of experimental surgery. It has chapters on the antivivisection movement, and the care and feeding of animals in addition to chapters on anesthesia; equipment, technic, sutures and instruments; and 24 addition chapters covering nearly all of the phases of experimental surgical technic. It is dedicated to Frank C. Mann with whom the author was formerly associated and has a foreword by Donald C. Balfour of the Mayo Clinic. In a pleasing epilogue Doctor Markowitz states "It is our wish that this book may become a contribution to the pedagogy of surgery and surgical craftsmanship."

The entire work is carefully done. Some of the descriptive work will, to the surgeon, seem unnecessary but this work was written as much or more for the student as for the surgeon. In addition it will serve as a handbook in many experimental laboratories where surgical procedures are constantly or occasionally being used. The discussion of gastro-intestinal and biliary operations is so complete that this volume may well serve to augment and refresh the clinical surgeon's knowledge of the technic of these operations. Of course many of the operations must necessarily differ from similar procedures in man because of differences in anatomic arrangement, but the principles remain the same. Such chapters as "The Experimental Production of Chronic Peptic Ulcer" and much of the discussion of operations on the bowel, biliary tract and pancreas are offered as methods of experimental approach to problems which constantly concern the surgeon. The illustrations are excellent and profuse. The author has wisely chosen the best illustrations from many existing works on related subjects but he has added a goodly number of original drawings. Occasional typographical error (such as the misspelling of Reverdin in the legend under Figure 130) can easily be forgiven in so excellent a work which will be welcomed by research workers, students and clinicians interested in the experimental approach to surgical problems. I. R.

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[illegible] literature. H. M.

Archiv für Kreislaufforschung. Beihefte zur "Zeitschrift für Kreislaufforschung." Band 1, Heft 1-6 (July, 1937), 7-8 (Oktober, 1937). Editor: Dr. Eb. Koch, Professor of Physiology, Kerckhoff-Herzforschungs-Institut Bad Nauheim, and Dr. Ed. Stadler, Professor and Attending Physician, City Hospital of Plauen. Dresden: Theodor Steinkopff, 1937. Pp. Heft 1-6, 224; illustrated; Heft 7-8, 80, illustrated.

This new Journal, the first number of which was published in July 1937, is to be supplementary to the Zeitschrift für Kreislaufforschung. Its the circulation and also to include critical reviews dealing with important circulatory problems.

The first issue contains 3 articles. The article by Max Holzmann covers 170 pages and deals with studies on chest leads in electrocardiography. The American work on this subject is confirmed. The second article by Professor Karl Hasebroek deals with the function of capillaries of organs in their relationship to the circulation of blood. The third article by Hans Havlicek attempts to support the thesis that the heart operates as a hydraulic ram rather than a pressure pump. C. W.

DIE IRRADIATION AUTONOMER REFLEXE. Untersuchungen zur Funktion des autonomen Nervensystems. By DR. ALFRED SCHWEITZER, Assistant in Department of Physiology, Middlesex Hospital Medical School, University of London. (The Radiation of Autonomic Reflexes. A contribution to the function of the autonomic nervous system.) Pp. 376; 38 illustrations. Basel: S. Karger, 1937. Price, Paper, Fr. 40; Bound, Fr. 44.

THIS book presents a strange and perplexing mixture of facts and speculations. The leading idea of the book is that stimulation of one portion of the autonomic (animalic) nervous system may spread over wide areas of both these systems. This radiation of autonomic reflexes is governed by certain rules. For example, the arterial blood pressure, acting over the pressoreceptors, influences not only "the vasomotor apparatus of the whole organism and the various activities of the heart, but also the function of the gastro-intestinal tract, the cranial and sacral parasympathetics, the endocrine glands, blood volume and composition, muscle tonus and somatic reflexes." A very useful compilation of the literature, bearing on the subject, aids in the task "to summarize the manifold viewpoints, collected in the various branches of science and to detect the laws of the experimental findings." The author tries to prove that "the radiation of autonomic reflexes is a normal property of the vegetative nervous system, founded in the organization and function of the nervous substance." Terms like the "tonus" of the sympathetic and parasympathetic system play a large rôle in the deductions. "It is the function of the sympathetic nervous system to guarantee the actual mechanical power, whereas the parasympathetic nervous system manages the energy reserves, rebuilds the used up stocks and maintains the potential preparedness of the organism." These and a number of similar generalized statements open interesting perspectives but do not seem justifiable on the ground of our present knowledge of facts nor helpful in further studies. The complicated diction of the book does not facilitate reading. F. L.

FEVER THERAPY. Abstracts and Discussions of Papers Presented at the First International Conference on Fever Therapy, College of Physicians and Surgeons, Columbia University, New York City, March 29, 30 and 31, 1937. Edited by nine members of the American Committee: DR. WALTER M. SIMPSON, Dayton, Ohio, Chairman; DR. WILLIAM BIERMAN, New York City, Secretary. Pp. 483. New York: Paul B. Hoeber, Inc., 1937. Price, $5.00.

BEGINNING in 1931, there has been held in this country an Annual Conference on Fever Therapy. In March, 1937, there met in New York City, the First International Conference on Fever Therapy, attended by physicians from 16 countries, and with 13 nations represented by delegates officially appointed by Ministries of Health. The present volume contains abstracts and discussions, each printed in English, French and German, [illegible] 1930

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Heart Disease in General Practice. By Paul D. White, A.B., M.D., Assistant Professor of Medicine, Harvard University Medical School, [illegible] M.D. Pp. 358; 45 figures. New York: National Medical Book Company, Inc., 1937.

Syphilis, Gonorrhea and the Public Health. By Nels A. Nelson, B.S., M.D., F.A.P.H.A., Director, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health; and Gladys L. Crain, R.N., Epidemiologist, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health. Pp. 359; illustrated. New York: The Macmillan Company, 1938. Price, $3.00.

Diseases of the Blood. By Cyrus C. Sturgis, M.D., B.S., Professor of Medicine, University of Michigan Medical School; Director, Thomas Henry Simpson Memorial Institute for Medical Research, and Raphael Isaacs, A.B., A.M., M.D., Associate Professor of Medicine, University of Michigan Medical School; Assistant Director, Thomas Henry Simpson Memorial Institute for Medical Research. Edited by Morris Fishbein, M.D. Pp. 302, 2 figures. New York: National Medical Book Com-

The Truth About Childbirth. Lay Light on Maternal Morbidity and Mortality. By ANTHONY M. LUDOVICI. Pp. 294. New York: E. P. Dutton & Co., Inc., 1938. Price, $2.50.

Men Past Forty. By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by WINFIELD SCOTT PUGH, B.S., M.D. Pp. 154. New York: Harvest House, 1938. Price, $2.00.

This book written in popular terms attempts to explain sexual mechanisms in the male and many of their disorders. It suffers from the usual defects of this type of book but not glaringly so, and apparently has been written with proper motives.

Bile. Its Toxicity and Relation to Disease. By O. H. HORRALL, M.D., PH.D., F.A.C.S., Department of Physiology, The University of Chicago. Pp. 434. Chicago: The University of Chicago Press, 1938. Price, $4.00.

Hemorrhoids. By MARION C. PRUITT, M.D., L.R.C.P. S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., Associate in Surgery, Emory University School of Medicine; Proctologist, Grady, Crawford W. Long Memorial, and Georgia Baptist Hospitals, etc. Pp. 170; 73 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.00.

The Heart in Pregnancy. By JULIUS JENSEN, PH.D. (in MEDICINE), University of Minnesota, M.R.C.S. (ENGLAND), L.R.C.P. (LONDON), Assistant Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital; Physician to St. Louis Maternity and St. Louis City Hospitals. Pp. 371; 5 figures and 117 tables. St. Louis: The C. V. Mosby Company, 1938. Price, $5.50.

A History of Women in Medicine. From the Earliest Times to the Beginning of the Nineteenth Century. By KATE CAMPBELL HURD-MEAD, M.D. Pp. 569; illustrated. Haddam, Conn.: The Haddam Press, 1938. Price, $6.00.

NEW EDITIONS.

Hernia. Anatomy, Etiology, Symptoms, Diagnosis, Differential Diagnosis, Prognosis, and the Operative and Injection Treatment. By LEIGH F. WATSON, M.D., Member of Attending Staff of California Lutheran Hospital and Methodist Hospital of Southern California, Los Angeles. Pp. 591; 281 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1938. Price, $7.50.

A Text-Book of Pathology. An Introduction to Medicine. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 1064; 459 illustrations and 16 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

A Text-book of Pathology. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 894; 412 illustrations and 2 colored plates. Third edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $9.50.

Symptoms of Visceral Disease. A Study of the Vegetative Nervous System and Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif.; Professor of Clinical Medicine, University of Southern California, etc. Pp. 442; 87 illustrations and 10 colored plates. Fifth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $5.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY.

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FRANKLIN G. EBAUGH, M.D.
[illegible]

AND

GEORGE S. JOHNSON, M.D.
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PSYCHIATRIC FACILITIES IN THE GENERAL HOSPITAL.

During the past decade, psychiatric diagnostic, teaching and research facilities in the general hospital have contributed to a better understanding of the personal and interpersonal factors in illness.

Although a recent historical survey[1] revealed that psychiatric facilities were available in the Bellevue Hospital, New York City, and the Philadelphia General Hospital in the 19th century, the establishment in 1902 of a psychiatric pavilion in the Albany Hospital attracted considerable attention. In 1923, a psychiatric service was introduced in the Henry Ford Hospital. Heldt's program in the latter hospital has been of value in demonstrating the practical as well as the more academic advantages of this type of service.

In the opinion of the Reviewer the most significant progress in the present development is due to a number of excellent services now in operation in a number of university teaching hospitals. Muncie,[2] Rennie,[3,4] and Billings[5,6] have described the objectives, scope and methods of their work.

Obviously, the plan of operation in each hospital is dependent upon the ability and interest of the psychiatric personnel, the receptivity of the hospital non-psychiatric clinical staff and local conditions of hospital policy. For purposes of simplicity the various services may be divided into three types.

1. Psychiatric service outside the major clinical divisions of the hospital. This is known as a consultation service, which remains independent and has no formal attachment to medicine, pediatrics, surgery, obstetrics and gynecology. The most efficient services of this type are those in the Massachusetts General Hospital, Boston; Payne Whitney Psychiatric Clinic, New York City; the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore; and the New Haven Hospital, New Haven, Conn.

2. Psychiatric Service within the Department of Medicine, as exem-

plified by the work being done in the Columbia University group of hospitals, New York City.

3. Liaison organizations as operated in the Universities of Colorado and Michigan. The objectives of such programs are dependent upon the previously noted variables. *Ideally, the following objectives* should be reached.

(*a*) Educational program to nurses and hospital administrators.

(*b*) Supplementing the psychiatric education of medical students by the study of all cases which present major or minor personality disturbances with or without somatic illness.

(*c*) Education of the intern staff. Previous study (4a) revealed the need for psychiatric education in the general internship as part of the basic preparation for the practice of medicine.

4. Establishment of a rapprochement between psychiatry and the major clinical divisions of the hospital to further appreciation of the concept of personality in somatic illness.

5. Initiation of interdepartmental research in the field of psychosomatic relations.

6. Educational propaganda to the patient-public in the need to rid the latter of the omnipresent stigma of mental disease.

It is hoped that endeavors of this type will throw further light on a number of baffling clinical syndromes. The recent reviews of Dunbar[3] and Wittkower[12] have aided in drawing attention to some of the difficulties encountered in the study of psychosomatic relations.

Attention has been drawn to the more frequent personality disorders as they are encountered by the general practitioner.[4b] More specifically, the psychogenic aspects of thyrotoxicosis,[1c,6b,c] disorders of the gastro-intestinal tract,[6c,9a,b,10] and hypertension[6a] have been studied in various details.

In the field of pediatrics, Crothers[2] has considered a modification of present day pediatric services in order to adopt the more pertinent psychiatric principles necessary in understanding behavior problems in children who are somatically ill. Other suggestions have been offered in respect to surgery, obstetrics and gynecology.[4c,11]

It is hoped that the introduction of psychiatry into the general hospital will serve as a means of teaching nurses, students, interns and physicians the need for a more integrated approach to the sick person, as well as offering a fertile ground for further study of the psychogenic aspects of various clinical syndromes.

FRANKLIN G. EBAUGH, M.D.

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OTO-RHINO-LARYNGOLOGY.

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JOSEPH C. BECK, M.D.,

[illegible]

AND

M. REESE GUTTMAN, M.D.

[illegible]

RECENT PROGRESS IN OTONEUROLOGY.

Anatomy of the Central Vestibular Pathways. The anatomy of the [illegible] of the eighth nerve has been known for many years. The pathways of the central tracts of the auditory and vestibular nerves within the brain and the cortical end, have been the subject of much investigation and speculation since Bárány's epoch-making discoveries of [illegible] method of testing the labyrinth.

Lorente de Nó, on the basis of his experimental and anatomic studies, discusses the question as to whether the semicircular canals are represented by separate pathways in the brain stem as previously postulated by Jones and Fischer from their clinical observations. He states that all the fibers from the semicircular canals are parallel and the fact that they constitute two groups does not mean that each group corresponds to a canal as there are thin and medium fibers from all the canals in Group I and thick and medium fibers from all the canals in Group II. Each canal as well as the saccule is represented in every part of the vestibular nuclei and it is his opinion that the entire static labyrinth must be considered as a unit both anatomically and functionally.

Leidler, in reviewing the relations between the vestibular apparatus and the vegetative nervous system, believes there are connections between the descending tracts originating from the nucleus vestibularis and the nuclei intermediolateralis and nucleus intermediomedialis which form the autonomic cell groups of the spinal cord; there are also connections with the autonomic regions of the medulla oblongata, the mesencephalon and the diencephalon. Through these connections vestibular influences are exerted upon the pupil, vascular system, heart, respiration, digestion and metabolism.

Muskens sums up his work on the further connections of the vestibular nuclei which he calls the "supravestibular system." By this he means the posterior longitudinal bundle, the commissural nuclei (nucleus of the posterior commissure and the nucleus interstitialis) and the fibers running from these nuclei to the oral part of the opposite pallidum. The posterior longitudinal bundle is a highway containing both ascending fibers from the medial vestibular nuclei running to the posterior commissure and descending tracts from the pallidum by way of the commissure; these exert an influence upon forced movements in the lateral plane of the head and eyes both in man and in animals. Similar movements in the frontal plane are governed by other tracts in the posterior longitudinal bundle which have their first point of origin in the anterior vertical canal, while movements in the sagittal plane in animals are due to interruption of pathways which run from Deiter's nucleus through the cerebellum and by way of the superior peduncle to the pallidum. His work received a certain amount of support from the clinical studies of Shapiro[47a] on patients with oculogyric crises. Six of these were studied carefully from the vestibular standpoint both during their crises and in the intervals. After reviewing the literature and postmortem material available the latter came to the conclusion that these spasms can only be explained on the basis of Muskens' theories. He expressed the opinion that the pathways as outlined by Muskens are for the purpose of bringing tonic influences from the labyrinth to the pallidum and influencing movements of the head and eyes in various planes.

Aronson[1] continued the studies of Spiegel on the cortical terminations of the labyrinth. The latter had previously shown that after applying strychnine to various parts of the cerebral cortex convulsions resulted only after a rotation stimulus following strychnine application to the posterior ectosylvian and suprasylvian gyri. Even ablation of one labyrinth produced convulsions from drugging either side, so that the labyrinth was considered to have a bilateral representation. Aronson showed that after section of the posterior longitudinal bundle this phenomenon still took place, indicating that vestibular impulses can arrive at the cortex through other pathways.

Van Gehuchten[52] sums up his views of the anatomy of the central vestibular pathways. The primary arc of the vestibular system is formed by the vestibular nerve, the vestibular nuclei and their connection with other parts of the brain. The functions of the vestibular apparatus are the reflex assurance of the bodily equilibrium and the reflex control of the eye mechanisms. This is made possible through the connections with the spinal cord (fasciculus Deiterospinalis and descending fibers of the fasciculus longitudinalis posterior) as well as the connections with eye muscle nuclei (homolaterally through the fasciculus vestibulo-mesencephalicus, hetero-laterally through the ascending fibers of the fasciculus longitudinalis posterior). The vestibular apparatus is connected through the vestibulo-cerebellar fibers with the nucleus tecti; some fibers also run to the cerebellar cortex. The nucleus tecti is a vestibular coördinating center which unites vestibular impulses with those coming from the proprioceptive tracts. Connections exist between the vestibular system and the corpora striata probably by way of the ascending fibers of the fasciculus longitudinalis posterior, nucleus ruber and thalamus as well as from the globus pallidus and the commissural nuclei. Finally afferent and efferent connections with the cortex must exist.

Anatomy of the Central Cochlear Pathways. The central pathways leading from the cochlea have not been the subject of investigation to the extent of the vestibular pathways. Some workers, however, are recording progress in this field which offers enormous difficulties. Wiley[54] endeavored to determine which parts of the cerebral cortex are used to form and retain auditory stimuli. For this purpose he trained cats to respond to auditory stimuli and then subjected them to various small destructive lesions in the cortex. They were then retrained to their former level learning. Later they were killed and their brains carefully studied. Waley's results showed that the auditory mechanism is projected upon an area corresponding to *Luciani's area* which includes the posterolateral part of the cerebral cortex. Destruction of this area may cause an auditory deficit which, however, can be compensated. Brogden, Culler and their coworkers studied the localization of sound in the auditory tract of the guinea pig, as far as the medial geniculate body. They found that for purposes of learning, destruction of a single geniculate body equals the effect of destroying the cochlea or one-half of the cortex. They believe from their experiments that the frequencies follow a topographic formation from the cochlea which persists at least as far as the medial geniculate body. A number of interesting clinical observations in this field will be dealt with later in the review.

Physiology. The great stimulus given to the study of the function of the labyrinth by the discovery of the caloric reaction by Bárány, in 1906, made possible during the following decades for a notable advance in this field. The researches of Magnus and de Kleijn and others of the Utrecht school, as well as of Fischer and Wodak of Prague had clarified the complex activities of the labyrinth and established its essential character as an organ of reflex action. Several problems that still remained to be solved, however, will be touched upon here:

The Function of the Saccule. Students of the labyrinth had very early felt that the activities of the semicircular canals differed from those of the utricle and saccule, which had receptors of a somewhat different type (maculae) as well as otoliths in many species of animals. The former lent themselves much more readily to experimentation while isolated lesions of the latter proved difficult to produce until relatively recently. Nevertheless, the conviction persisted that the otolith organs evoked reflexes to changes in position as distinguished from the reactions to movement which could be readily demonstrated to belong to the semicircular canals. Subsequent experiments, however, indicated that of the two otolithic structures the utricle is by far the most important as far as the labyrinthine tonic-static reflexes are concerned. This is emphasized by de Kleijn and Versteegh.[210] Continuing their experiments on guinea pigs they found that tonic labyrinthine reflexes, as well as the reaction to rectilinear movements can still be obtained after destruction of the macula of the saccule. They believe that the first group of reflexes originate from the utricle and the second from the semicircular canals. Werner[53] believes as a result of his studies on the effect of changes in air pressure on the labyrinth of guinea pigs that the saccule serves to indicate the degree of atmospheric pressure. He found, following his experiments, changes in the cellular picture of the macula sacculi but not in that of utricular macula (to increases or decreases of atmospheric pressure). In a subsequent article he reviewed his work as well as that of others on the macula utriculi and came to the conclusion that this organ is the seat of the reflexes in response to change of position. He believes that the macula utriculi is differentiated anatomically to account for the multidirectional sensitivity to static changes. Ashcroft and Hallpike[3] isolated the saccular branch of the vestibular (in frogs) nerve and studied the action currents obtained in response to rotation or tilting of the animal as well as to vibrational stimuli; the former stimuli gave no response while the latter produced marked reactions. They believe that in man, as suggested by Tait, the saccule is concerned in the reception of bone-conducted sound.

The Origin of the Tonic-static Labyrinthine Reflexes. The rôle of the utricle in producing reactions to changes of position is doubtless of great importance. The belief, however, that the function of the semicircular canals is confined to "reactions of the head and eyes which occur during and after rotation, and reactions due to rectilinear accelerations" as summarized by Camis[10] as late as 1930, is no longer tenable in view of the work of McNally and Tait.[35] By a series of brilliant experiments in which separate canals as well as the utricle and saccule were ablated by severing the nerve outside the particular structure, these workers carried out a study of the functions of these organs in the frog. Their technique had the obvious advantage over other methods in that the effect could be confined with certainty to the desired canal or otolith organ. Their results indicated that the vertical canals as well as the utricle exerted a tonic effect upon the body musculature, especially that of the head. Loss of the anterior vertical canals resulted in marked loss of tonus on the part of the muscles involved in keeping the head up; loss of the posterior vertical canal resulted in an extended position of the head. They feel that each of the four vertical canals in the frog is a sentinel at its own portion of the head and that the vertical canals acting together with the utricles in control of the musculature of the head, body and limbs preserve the normal erect posture of the head during movement or while at rest. They found no evidence that the saccule partakes in equilibration. Hasegawa[25] repeated the centrifuging experiments by which Magnus and de Kleijn removed the otolithic membranes of guinea pigs and found that the tonic reflexes both in these animals and in frogs were still present after the otoliths were thrown off, thus lending further weight to McNally's experiments.

Reflexes to Rectilinear Accelerations. Hasegawa[25] also found that these reflexes were absent following the experiments just noted. This is in contradistinction to the conclusions of Camis that these reactions are due to stimulation of the semicircular canals and would indicate that the matter of assigning the exact origin of these reflexes is still open to discussion. The question is also discussed by Schubert.[45] His experiments indicated that in man at least rectilinear acceleration does not produce deviation of the endolymph and cupula within the semicircular canals.

Response of Statokinetic Apparatus to Sound. In the past, considerable controversy existed as to whether the semicircular canals have an auditory function. Although the nature of these structures has long been definitely established as peripheral organs of a proprioceptive nature, certain animal experiments, notably by Tullio and others, apparently tended to indicate that sound can be a stimulus for the semicircular canals. E. Huizinga[26] considered these experiments and repeated them with pigeons that had artificial openings made into their labyrinth after the cochlea had been destroyed, and obtained characteristic head movements which corresponded to different cristae when certain canals were plugged. Unlike Tullio, Huizinga found that the responses disappeared when the openings into the canal were closed. Gatteschi[illegible] elaborates on Tullio's theory as to the rôle of the combined cochlear and vestibular apparatus in orientation. He states that even in lower animals [illegible] such as [illegible] a [illegible] reaction occurs to sound stimuli. He considers that the cochlear, neck and vestibular reflexes cooperate in helping to determine the direction of sound, which is a matter of great importance for the animal.

The Hydrodynamic Theory of the Semicircular Canals. The hydrodynamic theory, which is largely held among students of vestibular physiology, considers that the stimuli which produce the reflexes arising from the semicircular canals are transmitted to the cristae as a result of an endolymph movement or tendency toward movement which in turn moves the cupula or jelly-like mass in which the hair cells are embedded. The bending of the cupula causes a pull upon the hair cells, thus producing the appropriate stimulus. This theory, which has been applied to explain both the phenomena resulting from rotation and from the caloric test, has been the subject of much discussion to the extent that even the existence of the cupula has been denied as an artefact. Wall,[illegible] using special method of staining and fixation on preparations fresh from the living animal, studied the cupula. He was able to demonstrate that it has a definite and unchangeable form, that it reaches from the crista to the roof of the ampulla and that it does not lie in contact with ampullar walls and roof. He was able to make pictures of artificial cupular deviations, using the methods of Steinhausen as described for the observation in the living animal. The experiments of the latter observer are of the highest importance. Using the semicircular canals of the pike and other animals, Steinhausen[16] injected India ink and observed the cupula through the ampullar wall. He demonstrated by means of a motion picture film that ordinary movements of the head, which resulted in a shift in change of the cupula produced compensatory ocular movements and that a flow of endolymph from such stimuli as the caloric test is only effective insofar as the pressure of the fluid causes a shift of the cupula. G. Dohlman,[17] using Steinhausen's technique with some modification, arrived at similar conclusions. He states that while the endolymph current acts only for a brief moment on the cupula in such tests as the rotation test, this structure takes about 20 seconds to recover its normal position and that during this time nystagmus persists; in the caloric test there is a constant pressure and a constant nystagmus.

The Relationship of the Labyrinth to the Vegetative and Vasomotor System. LeHeux and de Kleijn[21] studied the effect of unilateral extirpation of the labyrinth on the movements of the alimentary tract in cats, using roentgenograms. In one series, bilateral vagotomy was performed and in another the sympathetic fibers to the alimentary canal were severed. They concluded that the labyrinth exerts a definite influence upon the stomach and intestines and that this influence reaches these organs through the vagus. Cantele and Pais[12] studied the effect of passive congestion on the vestibular reflexes of guinea pigs. This was induced by hanging the animal's head down for varying lengths of time. They found that the reflexes first became diminished and finally disappeared, the last phenomena requiring 20 to 30 hours of suspension. When the normal position was resumed the vestibular reflexes returned even after experiments lasting several months. Microscopic examination of the labyrinth showed hemorrhages and edema to be much more marked in the cochlea than in the vestibular portion of the internal ear. In a previous article, Cantele[11] reviews the relationship between the labyrinth and the respiratory system on the basis of his own and others' researches. He states that caloric and mechanical irritation of the vestibular apparatus produces a reflex action characterized by negative blood pressure in the carotid and femoral arteries and that this reflex activity is probably carried by way of the tympanic plexus and the nervus intermedius. Destruction of the labyrinth is followed by some irregular oscillations in the respiratory curve. Muck[38] states that nystagmus due to vasomotor causes may occur spontaneously or may be produced by mechanical, thermal, or electric stimulation of the vertebral or radial arteries. An applicator which has been dampened with epinephrine will produce a white streak when passed along the inferior turbinate of such persons. He states that nystagmus not of labyrinthine origin can be made to disappear by stimulating the vertebral arteries, this supposedly being due to a disturbance of the blood supply in the region of Deiter's nucleus. The studies of Frazer[21] indicate that the vasoconstrictor impulses to the ear travel in the cervicosympathetic trunk and that no vasoconstrictor fibers reach the ear *via* the periarterial plexuses of the carotid or vertebral artery. This, from a theoretical standpoint would indicate a possible section of the cervicosympathetic trunk in certain cases of vertigo and tinnitus of vasomotor origin. From a practical standpoint, however, it is very difficult to differentiate between vestibular disturbances of local and central origin. Kotyza[29] demonstrates that stimulation of the vestibular apparatus exerts a considerable influence upon the vegetative system. The rotation test has a more pronounced effect upon the parasympathetic system, while the minimal caloric test decreases the tonus of the orthosympathetic system. Stimulation of the labyrinth by means of location is more marked than by the caloric test. Sudden stimulation of the vestibular apparatus increases the tonus of the vegetative nervous system and especially that of the parasympathetic system.

The Mechanism of Utricular Stimulation. The question as to whether the stimulus for the otolithic organs is constituted by the pull of the otolith upon the hair cells of the macula when the head is displaced from its accustomed position or by the pressure of the otolith is still a subject for discussion. Ulrich[51] carried out experiments on the exposed utricular otolith in a live pike. With a micromanipulator, which held a human hair, he moved the otolith about in various directions. He found that the only effective movements of the otolith in obtaining a reaction were either outwards or outwards and forwards. When the eye on the side of the stimulated utricle moved up the other one moved down. No downward movement of the homolateral eye could be produced by any movement of the otolith. Rotation about the longitudinal axis of the body to the left stimulated only the left labyrinth and rotation to the right only the right labyrinth.

The compensatory eye movements in response to change of position were tested by Gollas[17] in patients with one labyrinth destroyed. They were strapped on Grahe's table to eliminate neck reflexes and the fundus of the eye inspected with a special ophthalmoscope. The deviation of the papilla was noted in response to slow turning at 20, 40, 60 and 90 degrees from the midline and back again. Turning to the side on which the labyrinth had been destroyed gave a normal compensatory eye rotation; turning to the opposite side gave reduced ocular rotation. The author concluded that these eye movements in man are regulated chiefly by the contralateral labyrinth but also slightly by the homolateral one and that each labyrinth acts on both eyes.

Clinical Otoneurology. The past few years have been marked by an attempt to adapt tests of vestibular function in man in terms of everyday function, and in line with our knowledge of physiology of the labyrinth. There has been a noticeable trend away from the technique of the tests as elaborated by Bárány and taught by Jones and Fisher in this country, although these are still performed by many otologists here.

Compensatory Movements Tending to Preserve Equilibrium follow a characteristic pattern in animals with intact labyrinths. de Kleijn and Versteegh[23] found that after bilateral labyrinth extirpation in animals these reactions are absent following a quick tilt about the longitudinal axis. These reactions also do not occur in man if the usual vestibular reactions are absent. After loss of one labyrinth the tilt reaction is absent at first, later returns on one side and finally on both sides. From their animal experiments they believe that this reflex probably originates from the semicircular canals.

Rademaker,[63] who has made notable contributions towards the analysis of labyrinthine reflexes in animals, has for years attempted to apply his findings to the study of the vestibular apparatus in man. In a recent monograph he sums up his work in this direction. After reviewing and illustrating with serial photographs the reactions of animals to different types of falling, rotation and tilting either around a longitudinal or a bitemporal axis, he considers the reactions of the extremities to slow and rapid tilting in man when the patient is placed on his hands and knees (eyes closed) on a specially constructed bed. By means of photographs these are shown to bear a striking similarity to the reactions of animals. He studied about 80 patients with different intracranial and labyrinthine lesions and demonstrated conclusively that these reactions, which he terms the test of static adaption, are absent only in those instances where the peripheral or central vestibular apparatus is involved. This is invariably the case only with bilateral lesions; unilateral involvement does not give a uniform picture. Labyrinthine righting reactions and tonic reflexes on the eyes in response to a change in position (not movement) are considered to be of otolithic origin; they are present in man as well as in animals but are difficult to demonstrate except in infants and individuals with certain brain conditions, owing to the influence of the visual apparatus and the higher centers.

McNally[31] sums up his ideas on the application of tilting reaction to the study of the vestibular apparatus in man. These are based upon his extensive experiments previously mentioned as well as his clinical experience. He distinguishes between the "rapid tilt test" and the "slow tilt test." The first is primarily a test of vertical semicircular canal action but also to a lesser extent of "second mode" utricular action. The reactions take place in opposite directions. The canal action results in a compensatory reaction of the body musculature tending to send the body away from the tilt; the "second mode" utricular action tends to throw the body in the direction of the tilt. These reactions tend to some extent therefore to neutralize each other. The investigator should try to note whether there is a tendency to be thrown in the direction of the tilt (lesion of the vertical canals with intact utricle) or for overcompensation (lesion of utricle with intact vertical canals). Absence of the protective reaction would be due to loss of one or both labyrinths. The slow tilt as practised by Grahe is a test for "first mode" utricular action.

The Problem of Positional Nystagmus is one which has greatly interested clinical observers. It must be remembered that while compensatory eye movements in response to changed positions are known to be tonic reflexes of otolithic origin, no one has as yet succeeded experimentally in demonstrating that *nystagmus can be produced* by stimulation of the utricle or saccule. In spite of this fact, a strong belief has persisted among neurotologists that certain forms at least of positional nystagmus originate from the utriculo-saccular apparatus. Ruttin[44] reviews his experiences with the subject. He considers positional nystagmus and positional vertigo as of otolithic origin. Characteristic of pure positional nystagmus is a movement like the turning of a wheel; rotatory nystagmus is characteristic and can be called forth by bending. Vertical positional nystagmus he believes to be from the canals. The stimulus can come from either the diseased or the healthy side. He does not believe that neck reflexes can cause nystagmus. Seiferth[46] follows Ruttin's earlier classification of positional nystagmus into the type which follows a certain rule as to position required, direction of nystagmus, as well as intensity; the variety which follows no rule; and the nystagmus which shows the wheel-like turning noted above. The first and third varieties are of otolithic origin. Nystagmus is sought for with the aid of a magnifying glass in different positions. Positional nystagmus is to be differentiated from ordinary spontaneous nystagmus which is activated by change of position. The rotatory form of positional nystagmus is characteristic of peripheral disease. Positional nystagmus which follows no rule and changes its direction is typical for central involvement; that which follows a certain rule, for retrolabyrinthine and peripheral disease at its beginning. Exceptions to these general principles are not infrequent. In general, positional nystagmus is probably the first manifestation of a spontaneous nystagmus.

The Rotation Test. It has been recognized for a number of years, particularly abroad, that the technique of the rotation test as generally practised is open to very serious objections. The usual procedure of revolving the patient 10 times in approximately 20 seconds, besides constituting a maximal stimulus unlike anything which occurs under physiologic conditions, introduces a number of variable factors which decrease the value of the test. The initial acceleration, the speed of turning, and particularly the final retardation or stopping of the chair

[illegible]

[illegible]

that an angular acceleration of less than 0.25 degree per second per second (in an exceptional 0.09 degree per second per second) was sufficient to elicit a reaction. As to stimulation by rectilinear acceleration he considers that a difference in specific gravity between the cupula and the endolymph is essential towards stimulation. If this difference is greater than 1 part in 10,000 a rectilinear acceleration of 981 cm. per second (by gravity) would be sufficient to produce a reaction. Arslan[2] carried out experiments *on the effect of repeated rotation on the duration of post-rotatory nystagmus.* Using a chair with a rigid control of speed and a mechanical brake he found that the effect of repeated rotations is to cause a diminution of post-rotatory nystagmus as well as a lengthening of the latent period. He considered this fact to be due to interference phenomena in the vestibular centers. That central factors are important in post-rotatory nystagmus is further attested to by Mowrer.[40] Using pigeons, he found that if rotation experiments are preceded by a rest period during which the birds are hooded and immobilized, the duration of the nystagmus is markedly reduced. This seems to corroborate the observation of the effect of excitement on the character of the vestibular response in clinical practice. In another communication, Mowrer[40] reported the effect of repeated rotation with reduction in the duration of the nystagmus. Using hooded pigeons he found that this reduction did not affect the perching ability. This result corroborates through the laboratory the well-known observation that diminished nystagmus responses such as occur in acrobats or dancers is not synonymous with any lesion but may be an acquired condition. This type of experimentation, which opens a very interesting chapter, was begun several years ago by Griffith at the time when there was an attempt to set up arbitrary standards of "normal" responses with respect to nystagmus and other vestibular induced manifestations.

Caloric Test. This method of testing was radically changed when Kobrak demonstrated that very small quantities of water only a few degrees below body temperature could produce a vestibular reaction. The idea was so startling after the mass douches taught by Bárány that for a time this fact was used as an argument against the hydrodynamic theory of semicircular canal stimulation. How little the response is in accord with the type of caloric stimulus used is brought out by Fleischmann,[20] who performed a series of irrigations on the same subject to ascertain whether changes in temperature, the amount of fluid, and the length of time during which the ear is syringed influenced the extent of the reaction. He found that in the majority of instances no significant difference was present in the reaction. Various modifications of Kobrak's technique by Demetriades, Veits, Grahe and Frenzel are in use for the caloric test abroad, the mass douche having been practically abandoned except in this country. An important advance in the technique of studying both spontaneous and induced nystagmus was registered by the introduction of Frenzel's illuminated glasses which eliminate fixation by the patient and at the same time make the observation of the nystagmus much easier for the physician.

The Galvanic Test. The galvanic falling reaction was the subject of study by Blonder and Davis.[6] Using a balance board mounted on a low fulcrum they achieved a refinement of technique which made it possible to obtain a reaction from a patient with very small amounts of current, generally 0.5 to 2 ma. They tested 100 normal persons as well as a number of pathologic subjects. Of the latter, those with dead labyrinths gave no response even with 10 to 20 ma. of current; varying responses as to the amount of current required were obtained from the others.

Past-pointing. It is now several years since Fischer and Wodak showed that the pointing tests brought out by Bárány are complex reactions in which several elements, besides the vestibular stimulus achieved by the caloric or rotation tests, are of importance. Dorcus and Mowrer[18] made an experimental study of this test following rotation in persons under hypnotic suggestion and on normal subjects who knew that the object to which they were pointing was moving apparently in the same direction as the vertigo. They found past-pointing to be variable. They believe that patients try to correct both for post-rotational vertigo and for the tonic imbalance, which they think is sensed proprioceptively. Better results were obtained with a specially built board where the patient was not asked to point at any specific object, but by grasping certain pendants attached to the board and moving his arms following stimulation made an automatic record on a large sheet of paper which recorded the deviation. In this connection, it should be noted that the drift reaction with the outstretched arms, as elaborated by Wodak, in which the examiner sitting in front of the patient who has his eyes closed "lines up" his outstretched arms at the beginning of the test with those of the patient, is a simple and very sensitive substitute for the past-pointing test.

An investigation of the pointing test was also made by Behrman.[4] He pointed out that the method used for testing had considerable influence upon the result. If the arms are brought up there is a tendency in normal individuals for an outward drift from the midline which is somewhat greater in the right arm; when the arms are brought down no deviation or only a slight inward one is noted. Following stimulation, the drift of the arms is in accord with the principles brought out by Bárány but the degree of the deviation again depends upon the method of stimulation, and is greater when the arms are brought up than when they are brought down. The deviation from calorization gradually increases up to the tenth test and then decreases again gradually. He found that the method of testing determines which arm deviation will be more pronounced. After the cold caloric test the opposite arm deviation is the more pronounced while after warm water irrigation the homolateral one shows a greater drift. Rotation affects the opposite arm (to the rotation) the most. Large quantities of water give greater deviations than small ones and cold water is more effective than hot. The author feels that repeated stimulation tests in the same person give an added value to the pointing test. He found no definite relationship between the onset of dizziness and the degree of past-pointing and none between the direction of the apparent movement (of the vertigo) and that of the deviation. It may be pointed out that the last conclusion is in contradistinction to the teachings of Jones and his school in this country and is in accord with the physiologic principles brought in animal experimentation by Magnus and de Kleijn and in man by Fischer and Wodak indicating that the essential element in past-pointing induced by stimulation is a reflex activity of the musculature of the arms.

Vertigo. The cause of Ménière's symptom complex continues to furnish room for considerable discussion. There is still wide divergence of opinion as to the etiologic factors mainly involved. Eisenberg,[19] for example, studied 33 cases and came to the conclusion that while the condition is not a definite entity and may be due to different diseases, the immediate cause is due to a structural change in the nervous apparatus of the internal ear. Cohen,[13] on the other hand, found headache in all patients suffering from this condition and definite neurologic signs in 9 of his 11 cases. He feels that a primarily neurologic rather than a purely internal ear condition is suggested; in other words, that the cause of the vertigo is central. The borderline between so-called Ménière's symptom complex and attacks of vertigo due to other causes is often ill-defined. In a symposium on vascular disease, Shapiro[47b] gave the following groups of causes for vertigo due to circulatory disturbance:

1. Vasomotor instability without evidence of any structural abnormality in the blood-vessels; this, in his opinion, is the basis for most of the so-called Ménière's syndrome cases. Some of them show hemicranial headache and visual field disturbances at the time of the attack.
2. Blood dyscrasias which may cause vertigo through changes in the internal ear or through deficient oxygenation of the vestibular centers.
3. Circulatory disturbances accompanied by organic changes in the blood-vessels of the internal ear or brain, without or with hypertension, are apt to cause vertigo *on change of position* because the sclerosed vessels are unable to adjust themselves quickly to the effects of gravity, thus giving rise to a transient cerebral anemia.
4. Cardiac abnormalities with either a retarded or an accelerated pulse with mild cerebral anemia due to deficient heart action.

Two advances have been registered in the treatment of Ménière's syndrome. Furstenberg and his co-workers[22] tested out the theories brought forth some years previously by Dida Dederding on the rôle of disturbances of water balance due to abnormal sodium chloride intake in causing attacks of vertigo. They studied 14 cases of typical Ménière's syndrome which were hospitalized for 30 days or more. These patients were closely observed under various doses of sodium chloride as well as ammonium chloride which causes dehydration. They worked out a diet of which the features were a low content of sodium chloride with calories as needed, as well as considerable protein; vegetables and fruits were so regulated as to approach a neutral reaction from an acid-base standpoint. In addition, relatively large doses of ammonium chloride were administered periodically. This method of treatment gave good results.

Dandy[14] has sectioned the eighth nerve or its vestibular branch in a considerable number of patients suffering from Ménière's syndrome. He feels that the condition is due to some lesion of the nerve rather than in the end organ. The indication is furnished by repeated and intolerable attacks of dizziness with tinnitus and deafness which show no obvious cause and fail to yield to conservative treatment. While the claim of excellent results can no doubt be substantiated in the majority of cases, the Reviewer feels that caution in recommending the measure should be observed even where the presence of tinnitus seems to place the site of the lesion, as peripheral.

Labyrinthitis. The discussion as to the classification and proper methods of handling inflammation of the internal ear secondary to acute or chronic otitis media has occupied otologists for many years. The subject was apparently closed with Ruttin's exhaustive monograph 10 years ago, summarizing the literature and the experiences of the Neumann Clinic at Vienna. There has, however, since that time been noticed a trend towards further conservatism in managing these serious complications. This is emphasized by two important communications. Turner and Fraser[50] observed 216 cases of labyrinthitis in 14,479 cases of otitis media during a period of 25 years. Following Ruttin's classifications their indications for operation are as follows:

(*a*) Circumscribed labyrinthitis—radical mastoidectomy alone or with Hinsberg labyrinth operation if the hearing is poor.

(*b*) Serous labyrinthitis secondary to circumscribed labyrinthitis—radical mastoidectomy alone.

(*c*) Latent labyrinthitis—labyrinth operation at the time of the radical mastoidectomy if the latter is called for, but if the history indicates that the acute labyrinthine symptoms occurred more than 6 months previously, the labyrinth operation may be omitted.

(*d*) Acute serous labyrinthitis—if a simple mastoidectomy is not indicated the patient is put to bed and observed.

(*e*) Acute purulent labyrinthitis—if in the course of a chronic ear infection, a radical mastoidectomy plus the Hinsberg labyrinth operation is done; otherwise the patient is put to bed and watched for rise of temperature or headache.

Lund,[33] following much the same classification, summarized his experience at Copenhagen covering more than 500 cases of labyrinthitis over a period of 28 years. Like the preceding writer, he does not do a labyrinthectomy (as Ruttin indicated) on every case of chronic or latent diffuse labyrinthitis requiring a radical mastoid operation, nor on every patient with acute diffuse suppurative labyrinthitis. He maintains that every case of suppurative labyrinthitis will show a stage of meningeal irritation in the course of intracranial extension. If the patient is seen after a full blown meningitis has developed, labyrinthine operation is generally useless; if he is seen while the process is still confined to the internal ear, repeated observation of the cerebrospinal fluid will furnish the indication for operation. He operates when more than 2 cells per c.mm. are present in the spinal fluid. His statistics indicate that between 1921 and 1935 when these indications were followed for acute diffuse suppurative labyrinthitis is the best record—a mortality of only 31% of the entire period covered by the study was achieved.

Central Vestibular Disturbances. Nylen,[42] who previously studied spontaneous and positional nystagmus in a large group of brain tumors, reports on the symptomatology, from the vestibular standpoint, of experimentally induced brain tumors. He introduced into the cranial cavities of rabbits and rats laminaria tents or a small amount of Jensen's sarcoma, the former to cause a rapid, the latter a slow increase of intracranial pressure. He produced abnormal eye displacements, nystagmus and positional nystagmus which were manifested regardless of the location of the tumor, but were more marked when it was close to or in contact with the vestibular centers. The nystagmus was still present after destruction of both labyrinths; either the horizontal, rotatory or vertical form could be seen. The practical significance of the above study is to indicate in an experimental way the possible effect of remote tumors and other pressure-producing conditions within the cranial cavity upon the vestibular centers. This fact must always be borne in mind when attempting localization of tumors from vestibular symptoms.

A comprehensive study upon the relation of the frontal lobe to equilibrium is contributed by Delmas-Marsalet.[15] The report is of interest here as it tends to corroborate the cerebellar and vestibular connections which have been previously dwelt upon by Goldstein and others. Delmas-Marsalet indicates the existence of a connection between the prefrontal lobe and the crossed cerebellar hemisphere and between the prefrontal lobe and the homolateral vestibular nerve. He states that the frontal lobe appears to be a postural center for the neck and trunk. Disturbances of coördination due to frontal lobe lesions are rich in symptomatology but can be grouped under four heads: cerebellar, labyrinthine, prexic and gnostic. The labyrinthine symptoms are inclinations of the head and body toward the lesion, spontaneous past-pointing and deviation of the gait both toward the lesion. Various combinations of symptoms can occur and many frontal lobe lesions show no disturbances of coördination. He believes that the vestibular impulses probably reach the frontal lobe by way of the globus pallidus.

Beilin[5] studied the posture of the head in 12 cases of cerebello-pontine angle tumor all of whom but 1 had originated from the acoustic nerve. After discussing the various theories, Beilin came to the conclusion that as the head was turned in each case towards the side of the lesion the symptoms must be due to irritation of the vestibular centers in the brain.

Disturbances of Hearing Due to Central Lesions. A considerable increase in the number of clinical reports bearing upon this question has been noted within the past few years. Lawson[30] reported a tumor of the midbrain, extending partly into the left hemisphere, in which there was a hearing loss of about 12% in the right ear and about 60% in the left. Autopsy and previous examination revealed no other cause for the deaness. The finding of a homolateral deafness is not in accord with the teachings of observers abroad, such as Ruttin and Grahe, who indicated the loss to be either approximately equal on each side or more pronounced on the contralateral side—a finding which would be expected from the fact that most of the fibers which enter the brain stem, eventually cross to the opposite side. This thought is supported by the findings of Kompaneets,[28] who studied the hearing in 5 patients that had recovered from temporal lobe abscess. Both bone and air conduction were found to be reduced on the contralateral ear but chiefly for the low tones; hearing for conversations was not impaired. It must be said that most American observers have not been able to bring out the existence of central deafness. Neither Northington[41] nor McNally *et al.*,[36] in their study of brain tumors, could establish that deafness existed in these conditions excepting the ones involving the eighth nerve or the cerebello-pointine angle.

A notable contribution to this field is made by Brunner[9] on the basis of his experience and autopsies over fifteen years. He first disposed of the question as to whether a condition of stasis in the internal ear can occur analogous to the choking of the optic disk which is seen in increased intracranial pressure. He believes that this condition does not occur in consequence of a generalized intracranial hypertension but does occur at times in cerebello-pontine angle tumors as a result of compression of the two veins which carry the return flow from the internal ear. Relief of pressure in these circumstances will cause a return of the hearing (this has been noted by the Reviewer). Besides acusticus and cerebello-pontine angle tumors, tumors of the midbrain can cause deafness. This was first noted by Siebenmann. The hearing loss may be unilateral due to interruption of the contralateral pathway, or bilateral due to destruction of both secondary auditory pathways. Characteristically differentiating it from acusticus and cerebello-pontine tumor deafness is the hyperactive labyrinth which is present. Cerebellar tumors may also occasionally cause deafness. Brunner feels that, although the hearing center is definitely located in the cortex of the temporal lobe, it cannot be said that the existence of deafness due to tumors in this area is established.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 18, 1938

Investigation of the Blood-vessels of the Finger by the Method of Pressure Analysis. ALAN C. BURTON (Eldridge Reeves Johnson Foundation, University of Pennsylvania). Observations upon the changes of the finger volume pulse when external pressure is applied to the finger may give information as to the reactions of the vessels of different categories of the vascular tree. Though indirect, the evidence so obtained is statistical for all vessels present of a given class, while in the more direct methods only a few representative vessels can be observed.

The pressure within a plethysmographic cuff placed on the middle phalanx is quickly raised above systolic pressure and allowed to fall steadily to zero while the pulsations of finger volume are recorded photographically by a mirror oscillometer. From the record the amplitude of pulsation is then plotted against the pressure in the plethysmograph.

Similar procedure on a single artery gives a characteristic pulsation-pressure curve with a single maximum at about the diastolic pressure, determined by application of the various diastolic criteria to the wave form. The finger, however, gives curves showing several peaks of variable height but fairly constant occurrence. The various curves can, in general, be analyzed as made up of 5 components, which are tentatively associated with different groups of vessels, namely the veins, the capillaries, arterioles, arterial network and digital arteries. Changes of wave form and diastolic criteria seen to apply at more than one pressure suggest the progressive shifting of the origin of the pulsation as the cuff pressure falls.

Changes in the height and position of the component peaks of pulsation with reflex constriction and dilation and their position in the hypertensive are consistent with this interpretation.

Confirmation is found in the decreases of finger volume as the cuff pressure is steadily raised. These occur in discrete steps at pressures which coincide with the 5 component peaks of pulsation.

Respiratory Transport by the Blood of Some Fresh Water Fish. E. C. BLACK and LAURENCE IRVING (Martin Biological Laboratory, Swarthmore College). *On account of the natural variations in pressure of O_2 and CO_2 in fresh water with place, depth, and season, environmental conditions for the respiration of fish differ from the constant conditions in air.* The average O_2 capacity of blood of the carp at 15° is, 13.1 c.cm. per 100 c.cm., of corpuscles 41 c cm.; of the sucker, 10.4 c.cm. for blood, 35 c.cm. for corpuscles.

The curves relating O_2 content to O_2 pressure are not sigmoid but hyperbolic in form. CO_2 at small pressures reduces the O_2 capacity and prevents saturation even at O_2 pressures of 200 mm. In the blood of carp, the pressure of O_2 necessary for 50% saturation is increased by 1 mm. for each mm. pressure of CO_2. In the sucker, 1 mm. CO_2 raises the pressure of O_2 for half saturation by 6.0 mm. The CO_2 effect is reversible.

Changes in pressure of CO_2 are more important in O_2 transport than in mammalian blood in which at 50% saturation 3.5 mm. CO_2 increases O_2 pressure by only 1 mm., and the observed variations of CO_2 in natural waters would determine the possibility of respiration of these fish.

The CO_2 effect differs from the Haldane effect in mammalian blood. In the fish blood, acid causes anomalous swelling of corpuscles, fluoride and oxalate diminish the CO_2 effect, and hemolysis with saponin destroys the CO_2 effect. It seems attributable to a membrane or permeability condition which influences the hemoglobin by changing the ions within the corpuscle.

The Diabetogenic Action of the Anterior Pituitary. EVERETT IDRIS EVANS (Laboratory of Physiology, University of Chicago). Studies have now been completed on 24 normal and 7 "Houssay" dogs. Diabetogenic extracts have been made, using the extraction of beef anterior pituitary by strong alkali, in the cold. It has been possible to produce marked diabetogenic effects in 16 normal dogs and in each of the Houssay animals; 8 normal dogs proved refractive.

Data are now available on the effect of this extract on the blood sugar, total lipoids, pH and total CO_2, urine sugar, urine volume and glucose tolerance, of normal dogs. The blood sugar (fasting) rises to 160 to 533 mg. % in 4 to 5 days, stays elevated for about 5 days, to return sharply to a subnormal level on about the 10th to 12th day. The subnormal level (35 to 70 mg. %) is maintained for 4 to 6 days.

The total lipoids of the blood may rise to 9.5% on a low fat intake. The usual level is about 1.5 to 2.5%. On the 5th to 6th day, when the blood sugar is high (400–500 mg. %), the pH may fall to 7.35 and the total CO_2 to 30 vol. % and the acidosis may have to be relieved by insulin and alkalies.

In certain animals, the sugar output in the urine may rise to 45–55 gm. daily at the peak of the hyperglycemia, with the animals on a low sugar intake. Polyuria and polydipsia was noted in all 16 affected animals. Death in coma resulted in 2 animals with marked, untreated hyperglycemia.

Marked diabetogenic activity was found on injection of highly purified Prolactin (33 units/mg.) in doses of 0.4 and 1.0 mg./kilo in 2 Houssay dogs.

It is evident that normal dogs after 25 to 30 days of injections, with fasting normal blood sugars, show markedly abnormal glucose tolerance curves. They may be said to be in a "pre-diabetic" state. This agrees well with the findings of Young, on the production of a permanent diabetes with anterior pituitary extracts.

Correction. In the article by John B. Youmans and Marvin B. Corlette on "Specific Dermatoses Due to Vitamin A Deficiency" appearing in the preceding issue of this JOURNAL (May, p. 644) Figures 3 and 5 have been interchanged. Figure 3 should designate "after" treatment and Figure 5 "before" treatment. EDITORS.

NOTE ON ARTICLE ON "RUBBER SHEATHS AS VENEREAL DISEASE PROPHYLACTICS: THE RELATION OF QUALITY AND TECHNIQUE TO THEIR EFFECTIVENESS." (*Am. J. Med. Sci.*, **195**, 155, 1938.)

WE have been asked by the Charles A. Weeks Advertising Company to publish the following statement from the originator of "Sanitube," mentioned in the article by Messrs. Randolph Cautley, Gilbert W. Beebe, and Robert L. Dickinson, M.D., New York City.

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